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(54) Title: DIKETODIAZACYCLIC COMPOUNDS, DIAZACYCLIC COMPOUNDS AND COMBINATORIAL LIBRARIES THEREOF

(57) Abstract

The synthesis of individual di- and tri-substituted-1,4-diazacyclic compounds having 6- to 8-atoms in the cyclic ring, their corresponding 1,6-diketo-2,5-diazacyclic compounds and similar 1,4-diazacyclic ring compounds having one ring carbonyl group and 6-8 atoms in the ring is disclosed, as are libraries of such compounds. Methods of preparing and using the libraries of compounds as well as individual compounds of the libraries are also disclosed.

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DIKETODIAZACYCLIC COMPOUNDS, DIAZACYCLIC COMPOUNDS AND COMBINATORIAL LIBRARIES THEREOF

Description

Cross-Reference to Related Application

This is a continuation-in-part of application Serial No. 745,793, filed November 7, 1996 and now U.S. Patent No. 5,786,448.

Technical Field

The invention relates to the synthesis of individual di- and tri-substituted-1,4-diazacyclic compounds having 6- to 8-atoms in the cyclic ring, their corresponding 1,6-diketo-2,5-diazacyclic compounds and similar 1,4-diazacyclic ring compounds having one ring carbonyl gorup and 6-8 atoms in the ring, and libraries of such compounds. The present invention further relates to methods of preparing and using the libraries of compounds as well as individual compounds of the libraries.

Background Art

Heterocyclic compounds having a high degree of structural diversity have proven to be broadly and economically useful as therapeutic agents. [For reviews on solid phase organic synthesis, see: (a) Gallop, M. A. et al., *J. Med. Chem.*, 1994, 37, 1233. (b) Gordon, E. M. et al., *J. Med. Chem.*, 1994, 37, 1385. (c) Thompson, L. A. et al., *Angew. Chem. Int.*

Ed. Engl., 1996, 35, 17.(e) Hermkens, P. H. H. et al., *Tetrahedron*, 1996, 52, 4527. (f) Nefzi, A. et al., *Chem. Rev.* 1997, 97, 449.] A number of approaches have been reported for the solid phase synthesis of diketopiperazine derivatives: Gordon and Steele developed a strategy for the solid phase synthesis of diketopiperazines based on reductive amination on the solid support [Gordon, D. et al., *BioMed. Chem. Lett.*, 1995, 5, 47]. A similar approach has been published by Krchnàk and co-workers for the synthesis of persubstituted 2,5-diketopiperazines [Krchnàk, V. et al., In *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*; Chaiken, I. M., Janda, K. D. Eds., American Chemical Society: Washington, DC. 1996, pp 99-117], and Scott and co-workers developed an alternative strategy for the synthesis of a similar diketopiperazine library using bromocarboxylic acids and a range of amines [Scott, B. O. et al., *Mol. Diversity*, 1995, 1, 125].

The process of discovering new therapeutically active compounds for a given indication involves the screening of all compounds from available compound collections. From the compounds tested one or more structure(s) is selected as a promising lead. A large number of related analogs are then synthesized in order to develop a structure-activity relationship and select one or more optimal compounds. With traditional one-at-a-time synthesis and biological testing of analogs, this optimization process is long and labor intensive. Adding significant numbers of

new structures to the compound collections used in the initial screening step of the discovery and optimization process cannot be accomplished with traditional one-at-a-time synthesis methods, except over a time frame of months or even years. Faster methods are needed that allow the preparation of up to thousands of related compounds in a matter of days or a few weeks. This need is particularly evident when it comes to synthesizing more complex compounds, such as the 4,5-disubstituted-2,3-diketopiperazine and 1,4,5-trisubstituted-2,3-diketopiperazine compounds of the present invention.

Solid-phase techniques for the synthesis of peptides have been extensively developed and combinatorial libraries of peptides have been generated with great success. During the past four years there has been substantial development of chemically synthesized combinatorial libraries (SCLs) made up of peptides. The preparation and use of synthetic peptide combinatorial libraries has been described for example by Dooley in U.S. Patent No. 5,367,053; Huebner in U.S. Patent No. 5,182,366; Appel et al in WO PCT 92/09300; Geysen in published European Patent Application 0 138 855 and Pimmg in U.S. Patent No. 5,143,854. Such SCLs provide the efficient synthesis of an extraordinary number of various peptides in such libraries and the rapid screening of the library which identifies lead pharmaceutical peptides.

Peptides have been, and remain, attractive targets for drug discovery. Their high affinities

and specificities toward biological receptors as well as the ease with which large peptide libraries can be combinatorially synthesized make them attractive drug targets. The screening of peptide libraries has led to the identification of many biologically-active lead compounds. However, the therapeutic application of peptides is limited by their poor stability and bioavailability in vivo. Therefore, there is a need to synthesize and screen compounds which can maintain high affinity and specificity toward biological receptors but which have improved pharmacological properties relative to peptides.

Combinatorial approaches have recently been extended to "organic" or non-peptide libraries. The organic libraries to the present, however, are of limited diversity and generally relate to peptidomimetic compounds; in other words, organic molecules that retain peptide chain pharmacophore groups similar to those present in the corresponding peptide. Although the present invention is principally derived from the synthesis of dipeptides, the dipeptides are substantially modified. In short, they are chemically modified through alkylation, acylation, reduction, and cyclization into the subject diketopiperazines, thus providing mixtures and individual compounds of substantial diversity.

Significantly, many biologically active compounds contain diketopiperazines. Diketopiperazines are conformationally constrained scaffolds that are quite common in nature, and many natural products containing a diketopiperazine

structure have been isolated that encompass a wide range of biological activities. Included in such compounds are inhibitors of the mammalian cell cycle reported by Cui et al., *J. Antibiot.*, 47:1202 (1996), inhibitors of plasminogen activator-1, and topoisomerase reported by Charlton et al., *P. Thromb. Haeomast.*, 75:808 (1996) and Funabashi et al., *J. Antibiot.*, 47:1202 (1994). Diketopiperazines have been reported by Terret et al., *Tetrahedron*, 51:8135 (1995) to be useful as ligands to the neurokinin-2 receptor. Barrow et al., *Bioorg. Med. Chem. Lett.*, 5:377 (1996) found diketopiperazines to be competitive antagonists to Substance P at the neurokinin-1 receptor. Because, diketopiperazine moieties are found in many biologically active compounds and are known to have useful therapeutic implications, there is a need to further study and develop large numbers of 2,3-diketopiperazine compounds and their analogues of larger ring size.

This invention satisfies these needs and provides related advantages as well. The present invention overcomes the known limitations to classical organic synthesis of cyclic 2,3-diketopiperazines. Existing reported approaches for the synthesis of diketopiperazines describe only the synthesis of 2,5-diketopiperazines, the present invention provides a large array of diverse 1,4,5-trisubstituted- and 4,5-disubstituted-2,3-diketopiperazine compounds that can be screened for biological activity, related piperazine and larger

ringed compounds, as described below, that exhibit biological activity.

Brief Summary of the Invention

The invention provides a rapid synthesis of (1-substituted or 1,2-disubstituted)-(4-aminoalkyl)-1,4-diazacyclic compounds having 6- to 8-atoms in the cyclic ring and the corresponding 1,6-diketo-(2-substituted or 2,3-disubstituted)-(5-aminoalkyl)-2,5-diazacyclic compounds and related cyclic amino amides and cyclic keto diamines of Formula I, hereinafter, and further provides combinatorial libraries that contain those compounds. The naming system used herein is understood to not be in conformance with naming systems usually used in organic chemistry, and relies upon the structural features common to all of the contemplated compounds as is discussed below.

It is first to be noted that the contemplated compounds can have one of two structure types that each contain a cyclic compound in which two nitrogen atoms are present in the ring at what can be considered positions 1 and 4. The first compound type contains one or two carbonyl groups that can be bonded to a ring amine, in which the first amine contains another amine at the 2- through 7-position of an alkyl group bonded to that first amine, and in which the second amine also can also contain a substituent group. The second compound type contains the same structural features as the first type, but lacks the one or two carbonyl groups and is a cyclic

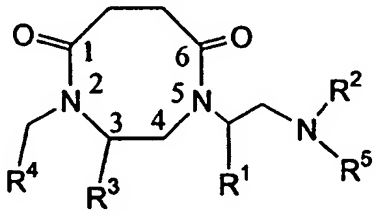
compound containing two nitrogen atoms at positions 1 and 4 of the ring.

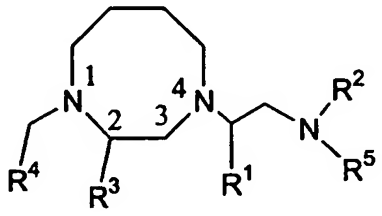
The numbering system used for these ring compounds begins with one of the carbonyl groups (when present) and continues around the ring to the second carbonyl group (when present) via the two ring nitrogen atoms so the ring nitrogen atoms have the same relative position numbers for all of the compounds embraced by Formula I. Thus, for a ring containing eight atoms and two amido carbonyls, the carbonyl groups are generically numbered to be at the 1- and 6-positions of the ring. The carbonyl groups and their amido nitrogen atoms of those compounds have the same numbers when the ring contains six atoms as in a diketopiperazine compound, even though the carbonyl groups of such a compound are assigned the 2- and 3-positions in a more usual system of nomenclature. Usual organic naming rules are followed for specific componds or libraries such as the 1,4,5-trisubstituted-2,3-diketopiperazines discussed in the examples.

A first of the ring nitrogen atoms of a compound of Formula I, below, is bonded to a C_1-C_7 alkyl group that contains an amine substituent at the 2- through 7-position from that first amine. For the two carbonyl group-containing compounds, that first ring nitrogen is at ring position 5. For the corresponding compounds lacking the two carbonyl groups, that same nitrogen is at the 4-position of the ring.

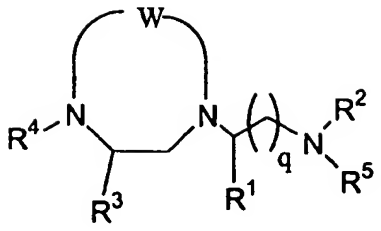
The second ring nitrogen can also be bonded to a substituent group. Using the above numbering system for the two carbonyl group-containing compounds, the second amine is at the 2-position for the group of compounds having the carbonyl groups and is at the 1-position for those compounds without the carbonyl groups. Compounds also typically contain a ring substituent at the 3-position of a dicarbonyl compound and at the 2-position of a cyclic diamine.

Exemplary structural formulas of some particularly preferred contemplated compounds are provided below based on structural Formulas II or III, hereinafter. Those formulas show the numbering system that is generally used, and in which q is one, and R^{a1} and R^{a2} and R^{b1} and R^{b2} are all hydrido and x and y are both one so that the ring positions are more easily seen.





More specifically, the present invention contemplates individual compounds and synthetic combinatorial libraries of those compounds in which the compounds have a structure corresponding to that shown in Formula I, below, or a pharmaceutically acceptable salt thereof:



I

wherein:

q is an integer having a value of 1-7;

W is a saturated or unsaturated chain of 2-4 carbon atoms that are bonded at each terminus of the chain to the depicted nitrogen atoms, wherein (1) zero, one or two of those carbon atoms of the chain is doubly bonded to an oxygen atom, (2)(a) each of the remaining carbon atoms of the chain is independently bonded to one or two substituents selected from the group consisting of a hydrogen atom (hydrido), C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) two of those remaining carbon atoms of the chain form a saturated or unsaturated mono- or bicyclic ring containing 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur.

R^1 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl,

phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group.

R^2 is selected from the group consisting of a C_1-C_{10} alkyl, C_2-C_{10} alkenyl, benzyl, substituted benzyl, naphthyl, or substituted naphthyl group and preferably is a methyl, ethyl, benzyl, allyl, or naphthylmethyl group, and more preferably is a 2-naphthylmethyl group. R^2 is most preferably a methyl or benzyl group.

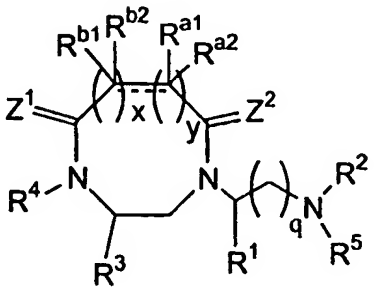
R^3 is selected from the group consisting of a hydrogen atom (hydrido), C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{16} phenylalkyl, C_7-C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group.

R^4 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} substituted alkyl, C_3-C_7 substituted cycloalkyl, C_7-C_{16} phenylalkyl, C_7-C_{16} phenylalkenyl, C_7-C_{16} phenylalkenyl and a C_7-C_{16} substituted phenyl-alkenyl group.

R^5 is selected from the group consisting of a hydrido, C_1-C_{10} acyl, aroyl, C_1-C_{10} alkylaminocarbonyl, C_1-C_{10} alkylthiocarbonyl, arylaminocarbonyl, and an arylthiocarbonyl group.

Another aspect of the invention contemplates individual compounds and synthetic combinatorial libraries of those compounds in which the compounds

have a structure corresponding to that shown in Formula II, below, or a pharmaceutically acceptable salt thereof:



II

wherein:

each of $=Z^1$ and $=Z^2$ is independently $=O$, or $=Z^1$ is $-R^{c1}$ and $-R^{c2}$ and $=Z^2$ is $-R^{c3}$ and $-R^{c4}$, wherein $-R^{c1}$, $-R^{c2}$, $-R^{c3}$ and $-R^{c4}$ are independently selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group.

x and y are independently zero or one, and the sum of x + y is zero, one or two.

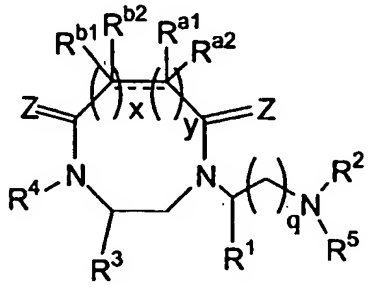
q is an integer 1-7.

The dotted line between the carbon atom of R^{a1} and R^{a2}, the carbon atom of R^{b1} and R^{b2} indicates the presence or absence (i.e., the possibility) of one additional bond between those depicted carbon atoms.

(a) R^{a1}, R^{a2}, R^{b1} and R^{b2} are independently selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) each of R^{a1} and R^{b1} is also bonded to the same saturated or unsaturated mono- or bicyclic ring containing 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur, or (c) one or both of R^{a1} and R^{a2} and R^{b1} and R^{b2} together are =O, and wherein both of R^{a2} and R^{b2} are absent when a double bond is present between the carbon atoms bonded to R^{a1} and R^{b1}.

Substituents R^1, R^2, R^3, R^4 and R^5 in Formula II are as described above for Formula I.

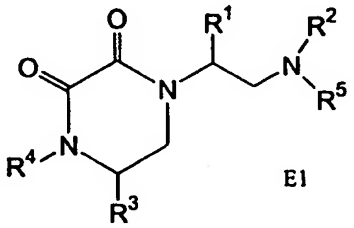
Another aspect of the invention contemplates individual compounds and synthetic combinatorial libraries of those compounds in which the compounds have a structure corresponding to that shown in Formula III, below, or a pharmaceutically acceptable salt thereof:



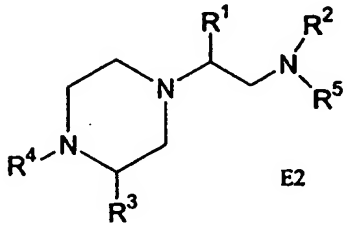
III

wherein =Z is =O or $(-H)_2$, R^{a2} and R^{b2} are hydrido or are absent, q, the dotted line, x, y, R^{a1}, R^{b1}, R^1, R^2, R^3, R^4 and R^5 have the meanings provided above.

Compounds and libraries in which q is one, and x and y are both zero are particularly preferred. These compounds correspond in structure to Formulas E1 and E2, below, wherein R^1, R^2, R^3, R^4 and R^5 are as defined above.



E1

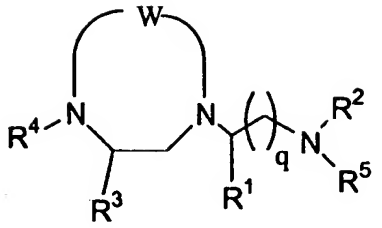


E2

R^5 is preferably hydrido in these compounds and libraries.

Detailed Description of the Invention

The present invention relates to individual compounds and synthetic combinatorial libraries of those compounds, as well as the preparation and use of those compounds and libraries, in which the compounds have a structure corresponding to that shown in Formula I, below, or a pharmaceutically acceptable salt thereof:



I

wherein:

q is an integer that is 1 through 7. Thus, for example, there can be one through seven methylene groups between the carbon bonded to the R^1 group and the nitrogen bonded to R^2 and R^5.

W is a saturated or unsaturated chain of 2-4 carbon atoms that are bonded at each terminus of the chain to the depicted nitrogen atoms, wherein (1) zero, one or two of those carbon atoms of the chain is doubly bonded to an oxygen atom, (2) (a) the remaining carbon atoms of the chain are independently bonded to one or two substituents selected from the group consisting of a hydrogen atom (hydrido), C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) two of those remaining carbon atoms of the chain form a saturated or unsaturated mono- or bicyclic ring containing 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur.

R^1 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-

C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group.

R^2 is selected from the group consisting of a C_1-C_{10} alkyl, C_2-C_{10} alkenyl, benzyl, substituted benzyl, naphthyl, or substituted naphthyl group and preferably is a methyl, ethyl, benzyl, allyl, or naphthylmethyl group. More preferably, R^2 is a 2-naphthylmethyl group, and R^2 is most preferably a methyl or benzyl group.

R^3 is selected from the group consisting of a hydrogen atom (hydrido), C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{16} phenylalkyl, C_7-C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group.

R^4 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} substituted alkyl, C_3-C_7 substituted cycloalkyl, C_7-C_{16} phenylalkyl, C_7-C_{16} phenylalkenyl, C_7-C_{16} phenylalkenyl and a C_7-C_{16} substituted phenylalkenyl group.

R^5 is selected from the group consisting of a hydrido, C_1-C_{10} acyl, aroyl, C_1-C_{10} alkylaminocarbonyl, C_1-C_{10} alkylthiocarbonyl, arylaminocarbonyl, and an arylthiocarbonyl group.

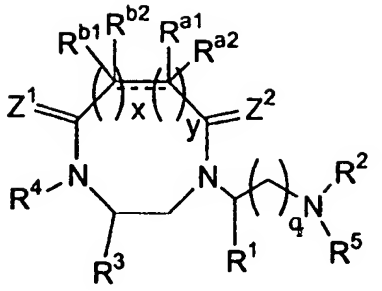
Looking more closely at W, it is seen that that group can contain a chain of two, three or four

carbon atoms, each of which can be substituted as described hereinafter. The terminal carbons of the chain are each bonded to one of the nitrogen atoms shown in Formula I so that the compound or library of compounds contains at least one ring that can contain six, seven or eight atoms in the ring.

The carbon chain W can also contain no unsaturated bonds between the carbon atoms, or can contain one double bond, and therefore is saturated or unsaturated.

The carbon chain W can also contain zero, one or two carbonyl [C=O] groups. When present, it is preferred that the one or two carbonyl groups be arrayed symmetrically between the two depicted nitrogen atoms. Preferably, when two carbonyl groups are present, each is bonded to a nitrogen atom forming two amide groups. When only one carbonyl group is present, that carbonyl group can be part of an amide group or as a keto group.

A more specific aspect of the invention contemplates individual compounds and synthetic combinatorial libraries of those compounds and their pharmaceutically acceptable salts in which the compounds have a structure corresponding to that shown in Formula II, below, or a pharmaceutically acceptable salt thereof:



II

wherein:

q is an integer that is one through seven;

each of $=Z^1$ and $=Z^2$ is independently $=O$ or $=Z^1$ is $-R^{c1}$ and $-R^{c2}$ and $=Z^2$ is $-R^{c3}$ and $-R^{c4}$, wherein $-R^{c1}$, $-R^{c2}$, $-R^{c3}$ and $-R^{c4}$ are independently selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

x and y are independently zero or one, and the sum of x + y is zero, one or two;

the dotted line between the carbon atom of R^{a1} and R^{a2} and the carbon atom of R^{b1} and R^{b2} indicates the presence or absence of one additional bond between those depicted carbon atoms, so that when present, the additional bond is shown as a solid line, following usual conventions of organic chemistry, and R^{a2} and R^{b2} are absent;

(a) R^{a1}, R^{a2}, R^{b1} and R^{b2} are independently selected from the group consisting of a hydrido, C_1-

C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) each of R^{a1} and R^{b1} is also bonded to the same saturated or unsaturated mono- or bicyclic ring that contains 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur, or (c) one or both of R^{a1} and R^{a2} and R^{b1} and R^{b2} together are =O, and wherein R^{a2} and R^{b2} are absent when a double bond is present between the depicted carbon atoms; and

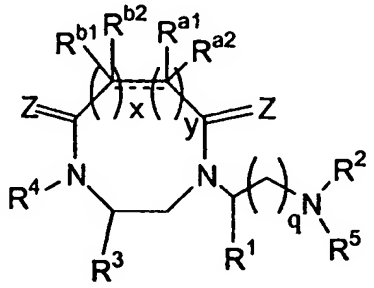
substituents R^1, R^2, R^3, R^4 and R^5 in Formula II are as described above for Formula I.

In one embodiment of a compound or library of Formula II, either or both of $=Z^1$ and $=Z^2$ is =O, so that a carbonyl group is present. In other embodiments of a compound or library of Formula II, $=Z^1$ and $=Z^2$ are the enumerated substituents $-R^{c1}$ and $-R^{c2}$ for $=Z^1$ and $=Z^2$ is $-R^{c3}$ and $-R^{c4}$ for $=Z^2$.

In addition to the specific substituents R^{a1}, R^{a2}, R^{b1} and R^{b2} of some embodiments, in other embodiments, R^{a2} and R^{b2} are each hydrido and R^{a1} and R^{b1} are each also bonded to the same saturated or unsaturated mono or bicyclic ring. In this instance, at least two fused rings are present, one is the ring shown in the formula and the second is bonded to R^{a1} and R^{b1}. That second ring can be monocyclic or

bicyclic and can contain 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur. Exemplary second rings include 1,2-cyclohexylidene, 1,2-cyclooctylidene, o-phenylene, 3,4-furanylidene, 2,3-pyrazinylidene, and 2,3-norbornenylidene. A double bond can also be present so that R^{a2} and R^{b2} are both absent.

Another aspect of the invention contemplates individual compounds and synthetic combinatorial libraries of those compounds and their pharmaceutically acceptable salts in which the compounds have a structure corresponding to that shown in Formula III, below, or a pharmaceutically acceptable salt thereof:



III

wherein:

q is an integer having a value of 1 through 7;

x and y are independently zero or one, and the sum of x + y is zero, one or two;

Z is an oxygen atom (=Z is =O) or two hydrido groups [=Z is $(-H)_2$];

the dotted line between the carbon atoms bonded to R^a and R^b groups indicates the presence or absence of one additional bond between those depicted carbon atoms, as before;

(a) R^{a1} and R^{b1} are independently selected from the group consisting of a hydrogen atom (hydrido), C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) R^{a1} and R^{b1} together with the depicted carbon atoms form a 5- to 8-membered saturated or unsaturated ring that contains zero to three heteroatoms that are independently oxygen, nitrogen or sulfur, and wherein R^{a2} and R^{b2} are are hydrido or are absent when a double bond is present between the depicted carbon atoms;

R^1 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^2 is selected from the group consisting of a C_1-C_{10} alkyl, C_2-C_{10} alkenyl, benzyl, substituted benzyl, naphthyl, or substituted naphthyl group and preferably is a methyl, ethyl, benzyl, allyl, or naphthylmethyl group. More preferably, R^2 is a 2-

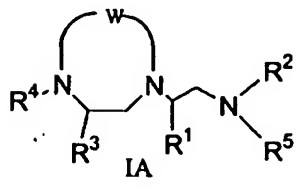
naphthylmethyl group, and R^2 is most preferably a methyl or benzyl group;

R^3 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{16} phenylalkyl, C_7-C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

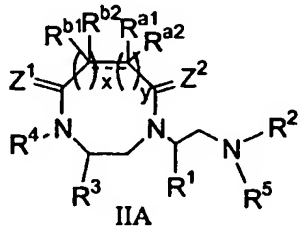
R^4 is selected from the group consisting of C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} substituted alkyl, C_3-C_7 substituted cycloalkyl, C_7-C_{16} phenylalkyl, C_7-C_{16} phenylalkenyl, C_7-C_{16} phenylalkenyl and a C_7-C_{16} substituted phenyl-alkenyl group; and

R^5 is selected from the group consisting of a hydrido, C_1-C_{10} acyl, aroyl, C_1-C_{10} alkylaminocarbonyl, C_1-C_{10} alkylthiocarbonyl, arylaminocarbonyl, and an arylthiocarbonyl group.

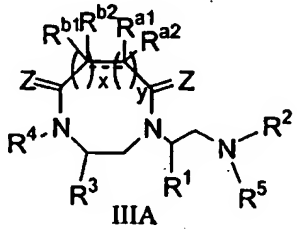
The value of q is preferably one or two in each of the above Formulas, and is most preferably one. Exemplary compounds of each of those compound types of Formula I, and particularly for Formulas II and III, where q is one are shown below as Formulas IA, IIA and IIIA.



IA

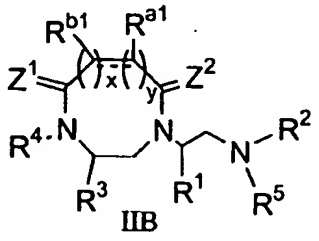


IIA

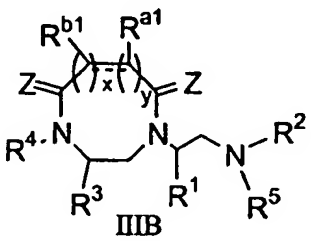


IIIA

In some preferred embodiments of Formulas II and III, R^{a2} and R^{b2} substituents are both hydrido or are absent because a doubls bond is present. In those embodiments, a contemplated compound corresponds in structure to Formula IIB or IIIB, below.



IIB



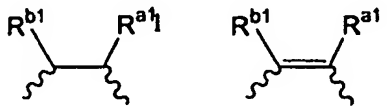
IIIB

In some preferred embodiments of compounds and libraries of Formulas IIB and IIIB, x and y are both zero so that the resulting compound is a diketopiperazine derivative. In other preferred embodiments, x and y are both one and R^{a2} and R^{b2} together with the depicted carbon atoms form a bond (so that the compound is unsaturated); or x and y are both one, R^{a2} and R^{b2} are absent and a double bond is present or are both hydrido, and each of R^{a1} and R^{b1} is bonded to the same saturated or unsaturated mono- or bicyclic ring containing 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen.

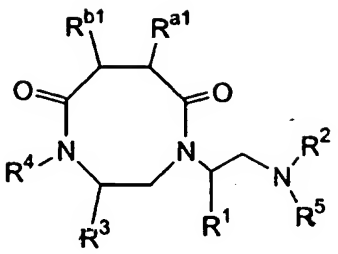
It is preferred that R^{a1} and R^{b1}, when present as individual substituents, both be identical to minimize the presence of isomers. It is similarly preferred when R^{a1} and R^{b1} are present as bonds to a saturated or unsaturated carbocyclic or heterocyclic

ring substituent that that substituent ring be symmetrically placed between the two ring nitrogen atoms.

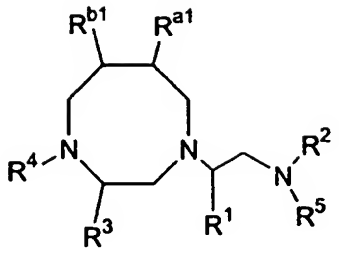
In addition, the carbon atoms to which the R^{a1} and R^{b1} groups are individually bonded can be bonded to each other via a single or double bond. Those two types of bonding are depicted in Formulas II and III by a single solid line, representing the single bond that must be minimally present, and one dotted line that represents another bond that can be present. Thus, with the remainder of the molecule represented by wavy lines, and R^{a2} and R^{b2} groups being hydrido and not shown or absent due to the presence of the double bond, the two contemplated bonds are



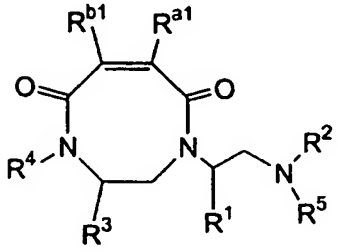
Exemplary compounds that are contemplated are illustrated below by the following structural Formulas B1 and B2 through U1 and U2, wherein R^{a2} and R^{b2} are both hydrido or are absent, R^{a1} and R^{b1} are a before-described substituent or together form a ring structure and the other R groups are as described before.



B1



B2



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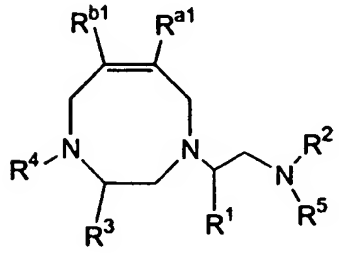

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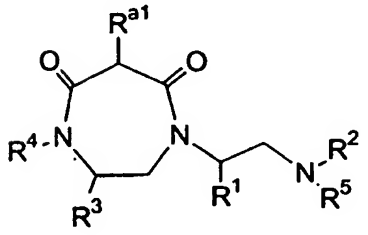
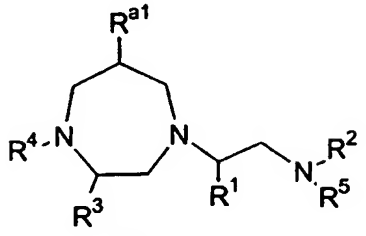


D1



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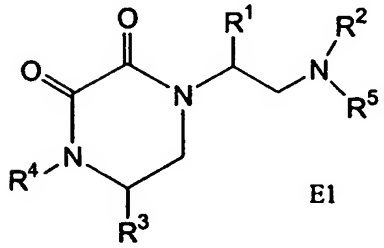
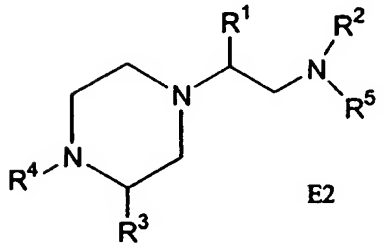


E1



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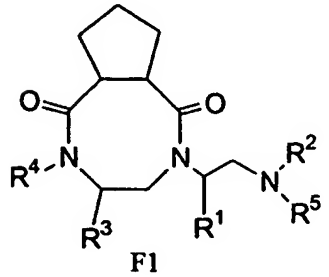

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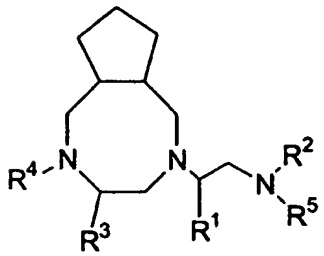
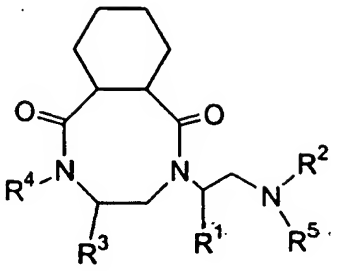


F2

5



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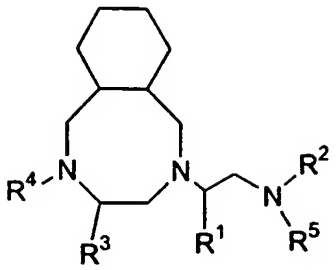

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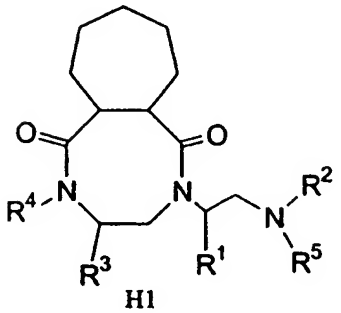

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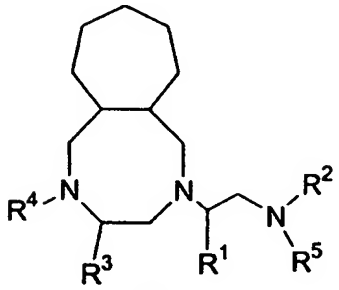

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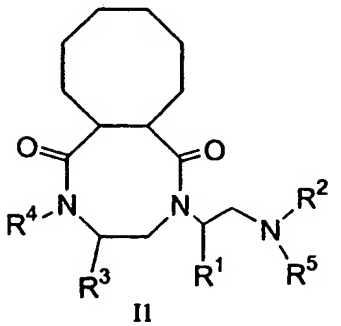

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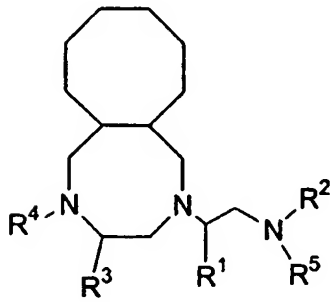

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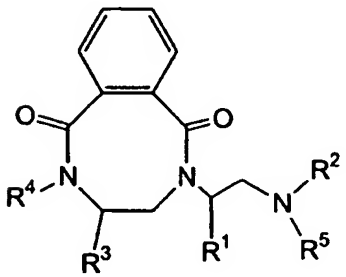

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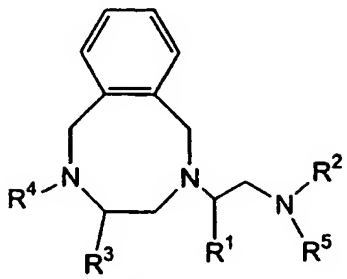

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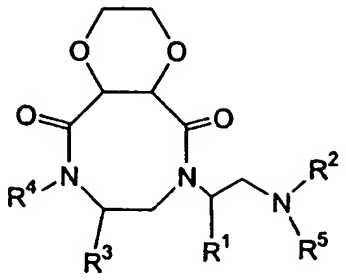

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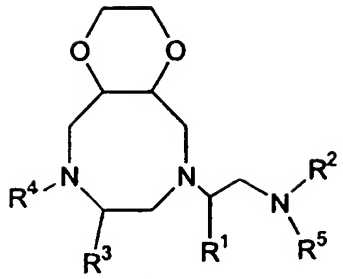

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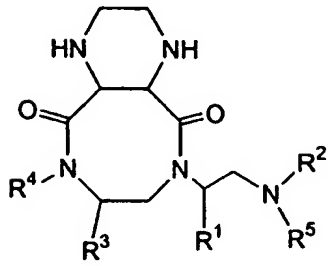

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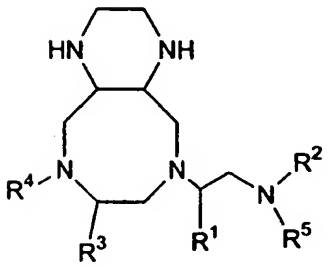

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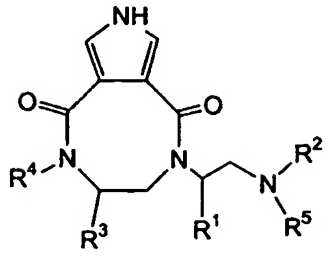

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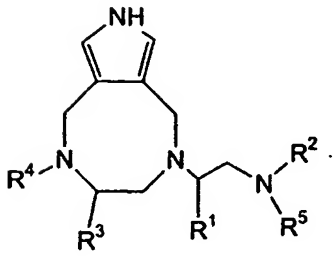

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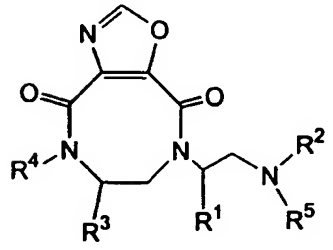

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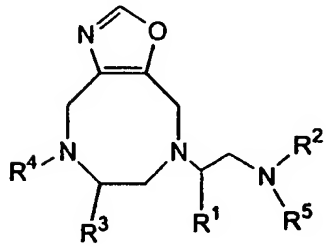

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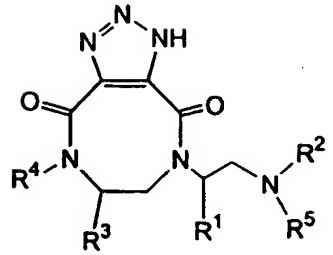

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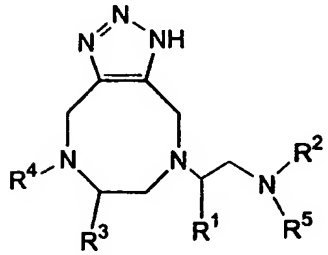

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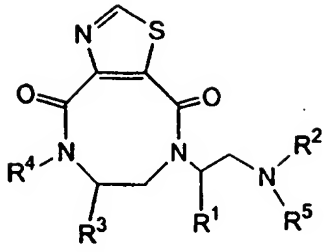

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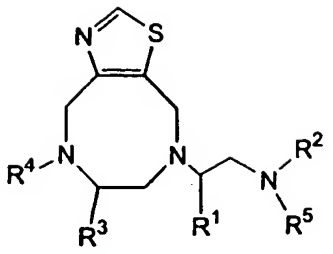

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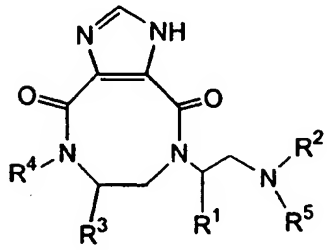

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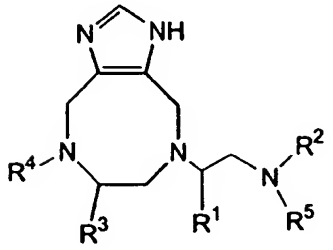

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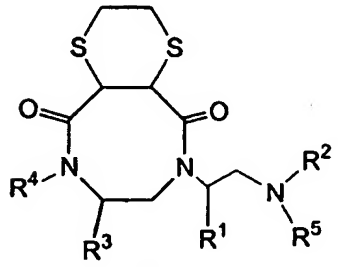

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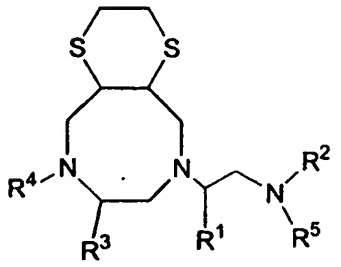

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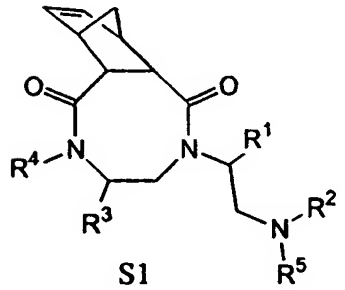

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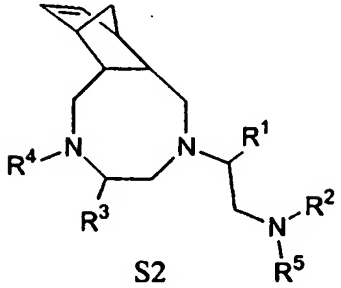
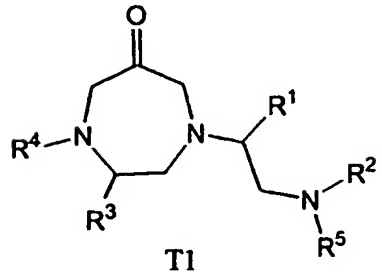


S2



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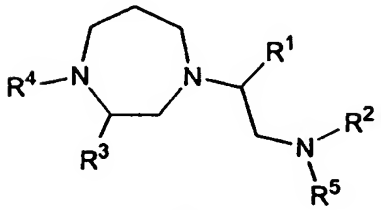
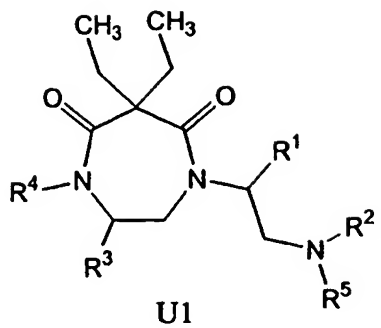


T2

5



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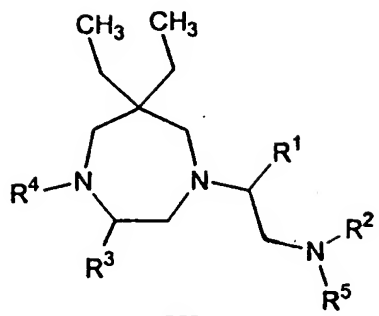


U2

In one embodiment of the above compounds and libraries,

R^1 is selected from the group consisting of a hydrido, methyl, benzyl, 2-butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, N-methyl,N-benzyl aminobutyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, N,N-dimethylaminoethyl, N,N-dimethylaminopropyl, N',N',N'-trimethylguanidinopropyl, N',N',N'-tribenzyl-guanidinopropyl, N',N'-dibenzylguanidinopropyl, N'-methylguanidinopropyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and a 4-imidazolylmethyl substituent;

R^2 is selected from the group consisting of a hydrido, methyl, ethyl, allyl, benzyl, or a 2-naphthylmethyl substituent;

R^3 is selected from the grop consisting of a hydrido, methyl, benzyl, 3-hydroxypropyl, 2-butyl, N-methylaminobutyl, aminobutyl, 2-methylpropyl, methylsulfinylethyl, guanidinopropyl, hydroxymethyl,

1-hydroxyethyl, 2-propyl, N-methyl-3-indolylmethyl, 4-methoxybenzyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, 2-naphthylmethyl, and a 4-imidazolylmethyl substituent;

R^4 is is selected from the group consisting of a 1-phenyl-1-cyclopropylmethyl, 2-phenylbutyl, 3-phenylbutyl, *m*-tolylethyl, 3-fluorophenethyl, 3-bromophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 4-fluorophenethyl, 3-methoxyphenethyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, 3-(3,4-dimethoxyphenyl)propyl, 4-biphenethyl, 3-phenyl-2-methyl-2-propenyl, 3-(2-trifluoro-methylphenyl)-2-propenyl, 3,4-dimethoxyphenethyl, 3,4-(dihydroxy)phenylethyl, 3-(2-methoxyphenyl)-2-propenyl, benzyl, 3-(4-chlorophenyl)-2-propenyl, *trans*-phenyl-2-propenyl, *m*-xylyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 3,5-bis-(trifluoromethyl)benzyl, butyl, heptyl, isobutyryl, (+/-)-2-methylbutyl, isovaleryl, 3-methylvaleryl, 4-methylvaleryl, 2-butenyl, 3-butenyl, *p*-xylyl, neopentyl, *tert*-butylethyl, cyclohexyl-methyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropyl-methyl, cyclobutyl-methyl, cyclopentylmethyl, 3-cyclopentylpropyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methyl-cyclohexylethyl, 2-methyl-2-butenyl, 1-adamantylethyl, 2-(α,α,α-trifluoro-*m*-toluidino)-3-pyridylmethyl, 4-nitrophenethyl, 4-(nitrophenyl)-butyl, 3-(4-nitrophenyl)-2-propenyl, 2-nitrobenzyl,

2,4-dinitrophenethyl, 4-biphenethyl, 2-chloro-5-nitrobenzyl, (4-pyridylthio)ethyl, 3,3-diphenylpropyl, 2-chloro-4-nitrobenzyl, 4-dimethylaminobenzyl, 4-nitrobenzyl, 3-dimethylamino-benzyl, abietyl, 2-methyl-4-nitro-1-imidizolylpropyl, *trans*-styrylethyl, cyclopentylethyl, 2,2-dicyclohexylethyl, (2-pyridylthio)ethyl, pentadienyl, 3-indolylethyl, 1-naphthylethyl, 3-(3,4,5-trimethoxyphenyl)propyl, 2-norbornylethyl, cyclopentylethyl, and a 2-ethylbutyl substituent; and

R^5 is a hydrido group, or an acyl group of a carboxylic acid selected from the group consisting of 1-phenyl-1-cyclopropane carboxylic acid, m-tolylacetic acid, 3-fluorophenylacetic acid, (α,α,α)-trifluoro-m-tolylacetic acid, p-tolylacetic acid, 3-methoxyphenylacetic acid, 4-methoxyphenyl-acetic acid, 4-ethoxyphenylacetic acid, 4-isobutyl-α-methylphenylacetic acid, 3,4-dichloro-phenylacetic acid, 3,5-bis(trifluoromethyl)phenylacetic acid, phenylacetic acid, hydrocinnamic acid, 4-phenyl-butyric acid, formic acid, acetic acid, propionic acid, butyric acid, heptanoic acid, isobutyric acid, isovaleric acid, 4-methylvaleric acid, trimethyl-acetic acid, tert-butylacetic acid, cyclohexane-carboxylic acid, cyclohexylacetic acid, cyclohexane-butyric acid, cycloheptanecarboxylic acid, acetic acid, cyclobutanecarboxylic acid, cyclopentane-carboxylic acid, cyclohexanepropionic acid, 4-methyl-1-cyclohexanecarboxylic acid, 4-tert-butyl-cyclohexanecarboxylic acid, 1-adamantaneacetic acid, 3,3-diphenylpropionic acid, dicyclohexylacetic acid,

indole-3-acetic acid, 1-naphthylacetic acid, 3-(3,4,5)-trimethoxyphenylpropionic acid, 2-norbornaneacetic acid, cyclopentylacetic acid, and 2-ethylbutyric acid.

In one of the preferred embodiments of the present invention of Formula III, where x and y are both zero, and q is one, R groups are those defined immediately below:

R^1 is selected from the group consisting of a hydrido, methyl, benzyl, 2-butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^2 is methyl;

R^3 is selected from the group consisting of a hydrido, methyl, benzyl, 3-hydroxypropyl, 2-butyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl,4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^4 is selected from the group consisting of a 1-phenyl-1-cyclopropylmethyl, *m*-tolylethyl, 3-fluorophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 3-methoxyphenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, butyl, heptyl, isobutyryl, isovaleryl, 4-methylvaleryl,

cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropyl-methyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-tert-butyl-1-cyclohexylmethyl, 4-methylcyclo-hexylethyl, 1-adamantylethyl, 3,3-diphenylpropyl, cyclopentylethyl, 2,2-dicyclohexylethyl, 2-indol-3-ylethyl, 1-naphthylethyl, 3-(3,4,5-trimethoxyphenyl)-propyl, 2-norbornylethyl, cyclopentylethyl, a 2-ethylbutyl substituent; and

R^5 is hydrido.

In another of the preferred embodiment of the present invention of Formula III, where x and y are both zero, and q is one, R groups are those defined immediately below:

R^1 is selected from the group consisting of a hydrido, methyl, benzyl, 2-butyl, N-methyl,N-benzylaminobutyl, N-methylaminobutyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl,hydroxymethyl, 1-hydroxyethyl, 2-propyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^2 is benzyl;

R^3 is selected from the group consisting of a hydrido, methyl, benzyl, 3-hydroxypropyl, 2-butyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl,4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^4 is selected from the group consisting of a 1-phenyl-1-cyclopropylmethyl, *m*-tolylethyl, 3-fluorophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 3-methoxyphenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, butyl, heptyl, isobutyryl, isovaleryl, 4-methylvaleryl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropyl-methyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclo-hexylethyl, 1-adamantylethyl, 3,3-diphenylpropyl, cyclopentylethyl, 2,2-dicyclohexylethyl, 2-indol-3-ylethyl, 1-naphthylethyl, 3-(3,4,5-trimethoxy-phenyl)propyl, 2-norbornylethyl, cyclopentylethyl, and a 2-ethylbutyl substituent; and

R^5 is hydrido.

In any of the above Formulas or other formulas herein, the stereochemistry of the chiral R^1 and R^3 groups can independently be in the *R* or *S* configuration, or a mixture of the two. For instance, as will be described in further detail below the R^1 and R^3 groups can be the side chains of the α-carbon of various amino acid residues. The amino acid residues can be in the L-or D-configuration, resulting in the same substituent group, R, varying only in its stereochemistry. In

addition, contemplated compounds can be present as diastereomers, as in the compounds of Formulas D1 and D2, in which case both isomers are contemplated.

In any of the Formulas herein, the term "C_1-C_{10} alkyl" denotes a radical such as a methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, hexyl, heptyl, decyl group and the like. The term "loweralkyl" denotes a C_1-C_4 alkyl group. A preferred "C_1-C_{10} alkyl" group is a methyl group.

The term "C_2-C_{10} alkenyl" denotes a radical such as a vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and decenyl group and the like, as well as dienes and trienes of straight and branched chains containing up to ten carbon atoms and at least one carbon-to-carbon (ethylenic) double bond.

The term "C_2-C_{10} alkynyl" denotes a radical such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, decynyl and the like, as well as di- and triynes of straight and branched chains containing up to ten carbon atoms and at least one carbon-to-carbon (acetylenic) triple bond.

The term "C_1-C_{10} substituted alkyl", "C_2-C_{10} substituted alkenyl" and "C_2-C_{10} substituted alkeynyl" denote that the above C_1-C_{10} alkyl group and C_2-C_{10} alkenyl and alkynyl groups are substituted by one or more, and preferably one or two, halogen,

hydroxy, protected hydroxy, C_3-C_7 cycloalkyl, C_3-C_7 substituted cycloalkyl, naphthyl, substituted naphthyl, adamantyl, abietyl, thiofuranyl, indolyl, substituted indolyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted) amino, (disubstituted) amino, guanidino, (monosubstituted)guanidino, (disubstituted)guanidino, (trisubstituted)guanidino, imidazolyl pyrolidinyl, C_1-C_7 acyloxy, nitro, heterocycle, substituted heterocycle, C_1-C_4 alkyl ester, carboxy, protected carboxy, carbamoyl, carbamoyloxy, carboxamide, protected carboxamide, cyano, methylsulfonylamino, methylsulfonyl, sulfhydryl, C_1-C_4 alkylthio, C_1-C_4 alkyl sulfonyl or C_1-C_4 alkoxy groups. The substituted alkyl groups can be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of the above substituted alkyl groups include the cyanomethyl, nitromethyl, chloromethyl, hydroxymethyl, tetrahydropyranyloxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl, allyloxycarbonylmethyl, allylcarbonyl-aminomethyl, carbamoyloxymethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, 6-hydroxy-hexyl, 2,4-dichloro(n-butyl), 2-amino(isopropyl), 2-carbamoyloxyethyl chloroethyl, bromoethyl, fluoroethyl, iodoethyl, chloropropyl, bromopropyl, fluoropropyl, iodopropyl and the like.

In preferred embodiments of the subject invention, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} substituted alkyl, C_2-C_{10} substituted alkenyl, or C_2-C_{10} substituted alkynyl, are more preferably C_1-C_7 or C_2-C_7, respectively, and more preferably, C_1-C_6 or C_2-C_6 as is appropriate for unsaturated substituents. However, it should be appreciated by those of skill in the art that one or a few carbons usually can be added to an alkyl, alkenyl, alkynyl, substituted or unsubstituted, without substantially modifying the structure and function of the subject compounds and that, therefore, such additions would not depart from the spirit of the invention.

The term "C_1-C_4 alkoxy" as used herein denotes groups that are ether groups containing up to four carbon atoms such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups. A preferred C_1-C_4 alkoxy group is methoxy.

The term "C_1-C_7 acyloxy" denotes a carboxy group-containing substituent containing up seven carbon atoms such as formyloxy, acetoxy, propanoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, and the like.

Similarly, the term "C_1-C_7 acyl" encompasses groups such as formyl, acetyl, propionoyl, butyroyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like.

The substituent term "C_3-C_7 cycloalkyl" includes the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl

or cycloheptyl rings. The substituent term "C_3-C_7 substituted cycloalkyl" indicates an above cycloalkyl ring substituted by a halogen, hydroxy, protected hydroxy, phenyl, substituted phenyl, heterocycle, substituted heterocycle, C_1-C_{10} alkyl, C_1-C_4 alkoxy, carboxy, protected carboxy, amino, or protected amino.

The substituent term "C_5-C_7 cycloalkenyl" indicates a substituent that is itself a 1-, 2-, or 3-substituted cyclopentenyl ring, a 1-, 2- , 3- or 4-substituted cyclohexenyl ring or a 1-, 2-, 3-,4- or 5-substituted cycloheptenyl ring, whereas the term "substituted C_3-C_7 cycloalkenyl" denotes the above C_3-C_7 cycloalkenyl rings substituted by a C_1-C_{10} alkyl radical, halogen, hydroxy, protected hydroxy, C_1-C_4 alkoxy, carboxy, protected carboxy, amino, or protected amino,

The term "heterocyclic ring" or "heterocycle" denotes an optionally substituted 5-membered or 6-membered ring that has 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen either alone or in conjunction with sulfur or oxygen ring atoms. These five-membered or six-membered rings can be fully unsaturated or partially unsaturated, with fully unsaturated rings being preferred.

Preferred heterocyclic rings include pyridino, pyrimidino, and pyrazino, furano, and thiofurano rings. The heterocyles can be substituted or unsubstituted as for example, with such substituents

as those described in relation to substituted phenyl or substituted naphthyl.

The term "C_7-C_{16} phenylalkyl" or "C_7-C_{16} aralkyl" denotes a C_1-C_{10} alkyl group substituted at any position by a phenyl ring. Examples of such a group include benzyl, 2-phenylethyl, 3-phenyl(n-prop-1-yl), 4-phenyl(hex-1-yl), 3-phenyl(n-am-2-yl), 3-phenyl(sec-butyl), and the like. A preferred C_7-C_{16} phenylalkyl group is the benzyl group. The term "C_7-C_{16} substituted phenylalkyl" denotes an above C_7-C_{16} phenylalkyl group substituted on C_1-C_{10} alkyl portion with one or more, and preferably one or two, groups chosen from halogen, hydroxy, protected hydroxy, keto, C_2-C_3 cyclic ketal phenyl, amino, protected amino, C_1-C_7 acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carbarnoyloxy, cyano, N-(methylsulfonylamino) or C_1-C_4 alkoxy, whose phenyl group can be substituted with 1 or 2 groups selecterd from the group consisting of halogen, hydroxy, protected hydroxy, nitro, C_1-C_{10} alkyl, C_1-C_6 substituted alkyl, C_1-C_4 alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, amino, (monosubstituted)amino, (disubstituted)amino, a N-(methylsulfonylamino) group, or a phenyl group that is itself substituted or unsubstituted. When either the C_1-C_{10} alkyl portion or the phenyl portion or both are mono- or

di-substituted, the substituents can be the same or different.

Examples of "C_7-C_{16} substituted phenylalkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)eth-1-yl, 2,6-dihydroxy-4-phenyl(n-hex-2-yl), 5-cyano-3-methoxy-2-phenyl(n-pent-3-yl), 3-(2,6-dimethylphenyl)n-prop-1-yl, 4-chloro-3-aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy(n-hex-1-yl), 5-(4-aminomethyl-phenyl)-3-(aminomethyl)(n-pent-2-yl), 5-phenyl-3-keto-(n-pent-1-yl), 4-(4-aminophenyl)-4-(I.4-oxetanyl)(n-but-1-yl), and the like.

The term "C_7-C_{16} phenylalkenyl". denotes a C_1-C_{10} alkenyl group substituted at any position by a phenyl ring. The term "C_7-C_{16} substituted phenylalkenyll" denotes a C_7-C_{16} arylalkenyl group substituted on the C_1-C_{10} alkenyl portion. Substituents can the same as those as defined above in relation to C_7-C_{16} phenylalkyl and C_7-C_{16} substituted phenylalkyl. A preferred C_7-C_{16} substituted phenylalkenyl is 3-(4-nitrophenyl)-2-propenyl. The term "substituted phenyl" specifies a phenyl group substituted at one or more positions, preferably at one or two positions, with moieties selected from the group consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_4 alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected

hydroxymethyl, amino, protected anlino, (moaosubstituted)amino, protected (monosubstituted) amino, (disubstituted)amino, trifluoromethyl, N-(methylsulfonylamino), or phenyl that is itself substituted or unsubstituted.

Illustrative substituents embraced by the term "substituted phenyl" include a mono- or di(halo)phenyl group such as 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono or di(hydroxy)phenyl groups such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected hydroxy derivatives thereof and the like; a nitrophenyl group such as 3-or 4-nitrophenyl, a cyanophenyl group for example, 4-cyanophenyl; a mono- or di(lower alkyl)phenyl group such as 4-methyl-phenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(iso-propyl)phenyl, 4-ethylphenyl, 3-(n-prop-1-yl)phenyl and the like: a mono or di(alkoxyl)phenyl, group for example, 2,6-dimethoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)-phenyl, 3-ethoxy-4-methoxyphenyl, 3-(4-methyl-phenoxy)phenyl, and the like; 3-or 4-trifluoro-methylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono-or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl;

a mono- or di(aminomethyl) phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl) phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different. For example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy- 4-chlorophenyl and the like are contemplated.

The term "substituted naphthyl" specifies a naphthyl group substituted with one or more, and preferably one or two moieties selected from the group consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1-C_{10} alkyl, C_1-C_4 alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted) amino, protected (monosubsticuted)amino, (disubstituted) amino trifluoromethyl, or N-(methylsulfonylamino). Examples of substituted naphthyl include 2-(methoxy)naphthyl and 4-(methoxy)naphthyl.

The term "substituted indolyl" specifies a indolyl group substituted, either at the nitrogen or carbon, or both, with one or more, and preferably one or two, moieties selected from the group consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10}

alkenyl, C_7-C_{16} phenylalkyl, C_7-C_{16} substituted phenylalkyl, C_1-C_6 alkoxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, monosubstituted amino, or disubstituted amino.

Examples of the term "substituted indolyl" includes such groups as 6-fluoro, 5-fluoro, 5-bromo, 5-hydroxy, 5-methyl, 6-methyl, 7-methyl, 1-methyl, 1-ethyl, 1-benzyl, 1-napthylmethyl, and the like. An example of a disubstituted indolyl is 1-methyl-5-methyl indolyl.

The terms "halo" and "halogen" refer to the fluoro, chloro, bromo, or iodo groups.

The term "(monosubstituted)amino" refers to an amino group with one substituent selected from the group consisting of phenyl, substituted phenyl, C_1-C_{10} alkyl, and C_7-C_{16} arylalkyl, wherein the latter three substituent terms are as defined above. The (monosubstituted)amino can additionally have an amino-protecting group as encompassed by the term "protected (monosubstituted)amino."

The term "(disubstituted)amino" refers to amino groups with two substituents selected from the group consisting of phenyl, substituted phenyl, C_1-C_{10} alkyl, and C_7-C_{16} arylalkyl wherein the latter three substituent terms are as described above. The two substituents can be the same or different.

The terms "(monosubstituted)guanidino, "(disubstituted)guanidino." and "(trisubstituted)-

guanidino" are used to mean that a guanidino group is substituted with one, two, or three substituents, respectively. The substituents can be any of those as defined above in relation to (monosubstituted)-amino and (disubstituted)amino and, where more than one substituent is present, the substituents can be the same or different

The term "amino-protecting group" as used herein refers to one or more selectively removable substituents on the amino group commonly employed to block or protect the amino functionality. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino nitrogen atom. In addition, the term "protected carboxamide" means there is an amino-protecting group present replacing the proton of the amido nitrogen so that there is no N-aLkylation. Examples of such amino-protecting groups include the formyl ("For") group, the trityl group (Trt), the phthalimido group, the trichloroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups. Urethane blocking groups, such as t-butoxy-carbonyl ("Boc"), 2-(4-biphenylyl)propyl(2)oxycarbonyl ("Bpoc"), 2-phenylpropyl(2)oxycarbonyl ("Poc"), 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenylethyl(1)-oxycarbonyl, 1.1-diphenylpropyl(1)oxycarbonyl, 2-(3,5-dimethoxyphenyl) propyl(2)oxycarbonyl ("Ddz"), 2-(p- 5 toluyl)propyl(2)oxycarbonyl, cyclopentanyl-oxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyl-oxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-

toluylsulfonyl) ethoxycarbonyl, 2-(methylsulfonyl)-ethoxycarbonyl, 2-(triphenylphosphino)-ethoxy-carbonyl, 9-fluoroenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl) ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benz-isoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl(2) propoxy-carbonyl, cyclopropylmethoxycarbonyl, isobornyl-oxycarbonyl, 1-piperidyloxycarbonyl, benzyloxycarbonyl ("Z"), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxy-carbonyl, α-2,4,5,-tetramethyl-benzyloxycarbonyl ("Tmz"), 4-methoxybenzyl-oxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chloro-benzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyIoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, and the like, the benzoylmethylsulfonyl group, dithiasuccinoyl ("Dts') group, the 2-(nitro)phenylsulfenyl group ("Nps'), the diphenylphosphine oxide group, and like amino-protecting groups. The species of amino-protecting group employed is usually not critical so long as the derivatized amino group is stable to the conditions of the subsequent reactions and can be removed at the appropriate point without disrupting the remainder of the compound. Preferred amino-protecting groups are Boc and Fmoc.

Further examples of amino-protecting groups embraced to by the above term are well known in organic synthesis and the peptide art and are

described by, for example. T. W. Greene and P. G. M. Wuts. Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons. New York. N.Y., Chapter 7, 1991. M. Bodanzsky. Principles of Peptide Synthesis. 1st and 2nd revised ed., Springer-Verlag, New York, N.Y., 1984 and 1993, and Stewart and Young. Solid Phase Peptide Synthesis, 2nd ed., Pierce Chemical Co, Rockford. IL 1984.

The related term "protected amino" defines an amino group substituted with an amino-protecting group discussed above.

The term "carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include 4-nitrobenzyl, 4-methoxy-benzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylene-dioxybenzyl, benzhydryl, 4,4'-methoxytrityl, 4,4',4''-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, t-butyldimethylsilyl, 2,2,2-trichloroethyl, β-(trimethylsilyl)ethyl, β-[di(n-butyl)-methylsilyl]ethyl, p-toluenesulfonylethyl, 4-nitrobenzyl-sulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)-prop-1-en-3-yl, and like moieties. The species of carboxy-protecting group employed is also usually not critical so long as the derivatized carboxylic acid is stable to the

conditions of subsequent reactions and can be removed at the appropriate point without disrupting the remainder of the molecule.

Further examples of these groups are found in E. Haslam, Protective Groups in Organic Chemistry, J. G. W. McOmie Ed., Plenum Press, New York, N.Y. Chapter 5, 1973, and T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley and Sons, New York, N.Y., Chapter 5, 1991. A related term is "protected carboxy", which refers to a carboxy group substituted with one of the above carboxy-protecting groups.

The term "hydroxy-protecting group" refers to readily cleavable groups bonded to hydroxyl groups, such as the tetrahydropyranyl, 2-methoxyprop-2-yl, 1-ethoxyeth-1-yl, methoxymethyl, β-methoxyethoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, benzyl, allyl, trimethylsilyl, (t-butyl)dimethylsilyl and 2,2,2-trichloroethoxycarbonyl groups, and the like. The species of hydroxy-protecting groups is also usually not critical so long as the derivatized hydroxyl group is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the compound.

Further examples of hydroxy-protecting groups are described by C. B. Reese and E Haslam, Protective Groups in Organic Chemistry, J. G. W. McOmie Ed., Plenum Press, New York, N.Y., Chapters 3 and 4, 1973, and T. W. Greene and P. G. M. Wuts, Protective Groups

in Organic Synthesis, 2nd ed., John Wiley and Sons, New York, N.Y., Chapters 2 and 3, 1991.

The substituent term "C_1-C_4 alkylthio" refers to sulfide groups such as methylthio, ethylthio, n-propylthio, isopropylthio, -butylthio, t-butylthio and like groups.

The substituent term " C_1-C_4 alkylsulfoxide" indicates sulfoxide groups such as methylsulfoxide, ethylsulfoxide, α-propylsulfoxide, iso-propyl-sulfoxide, n-butylsulfoxide, sec-butylsulfoxide, and the like.

The term "C_1-C_4 alkylsulfonyl" encompasses groups such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, α-butylsulfonyl, t-butylsulfonyl, and the like.

Phenylthio, phenyl sulfoxide, and phenylsulfonyl compounds are known in the art and these have their art-recognized definitions. By "substituted phenylthio", "substituted phenyl sulfoxide", and "substituted phenylsulfonyl" is meant that the phenyl can be substituted as described above in relation to "substituted phenyl."

The substituent terms "cyclic C_2-C_{10} alkylene", "substituted cyclic C_2-C_{10} alkylene", "cyclic C_2-C_{10} heteroalkylene." and "substituted cyclic C_2-C_{10} heteroakylene" defines a cyclic group bonded ("fused") to the phenyl radical. The cyclic group can be saturated or contain one or two double bonds. Furthermore, the cyclic group can have one or two

methylene groups replaced by one or two oxygen, nitrogen or sulfur atoms.

The cyclic alkylene or heteroalkylene group can be substituted once or twice by substituents selected from the group consisting of hydroxy, protected hydroxy, carboxy, protected carboxy, keto, ketal, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkanoyl, C_1-C_{10} alkyl, carbamoyl, C_1-C_4 alkoxy, C_1-C_4, alkylthio, C_1-C_4 alkylsulfoxide, C_1-C_4 alkylsulfonyl, halo, amino, protected amino, hydroxymethyl and a protected hydroxymethyl group.

A cyclic alkylene or heteroalkylene group fused onto the benzene radical can contain two to ten ring members, but it preferably contains four to six members. Examples of such saturated cyclic groups include a bicyclic ring system that is a 2,3-dihydroindanyl or a tetralin ring. When the cyclic groups are unsaturated, examples occur when the resultant bicyclic ring system is a naphthyl ring or indanyl. An example of a cyclic group which can be fused to a phenyl radical that has two oxygen atoms and that is fully saturated is dioxanyl. Examples of fused cyclic groups that each contain one oxygen atom and one or two double bonds occur when the phenyl ring is fused to a furo, pyrano, dihydrofurano or dihydropyrano ring. Cyclic groups that each have one nitrogen atom and contain one or two double more double bonds are illustrated where the phenyl is fused to a pyridino or pyrano ring. An example of a fused ring system having one nitrogen and two phenyl

radicals is a carbozyl group. Examples of cyclic groups that each have one sulfur atom and contain one or two double bonds occur where the benzene ring is fused to a thieno, thiopyrano, dihydrothieno, or dihydrothiopyrano ring. Examples of cyclic groups that contain two heteroatoms selected from sulfur and nitrogen and one or two double bonds occur where the phenyl ring is fused to a thiazolo, isothiazolo, dihydrothiazolo or dihydroisothiazolo ring. Examples of cyclic groups that contain two heteroatoms selected from oxygen and nitrogen and one or two double bonds occur where the benzene ring is fused to an oxazole, isoxazole, dihydroxazole or dihydroisoxazole ring. Examples of cyclic groups that contain two nitrogen heteroatoms and one or two double bonds occur where the benzene ring is fused to a pyrazolo, imidazolo, dihydropyrazolo or dihydroimidazolo ring.

One or more of the contemplated compounds within a given library can be present as a pharmaceutically-acceptable salt. The term "pharmaceutically-acceptable salt" encompasses those salts that form with carboxylate, phosphate or sulfonate anions and ammonium ions and include salts formed with the organic and inorganic cations discussed below. Furthermore, the term includes salts that form by standard acid-base reactions with basic groups (such as amino groups) and organic or inorganic acids. Such acids include hydrochloric, sulfuric, phosphoric, acetic, succinic, citric lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic,

d-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids.

The term "organic or inorganic cation" refers to counterions for the carboxylate, phosphate or sulfonate anion of a salt. The counter-ions are selected from the alkali and alkaline earth metals, (such as lithium, sodium, potassium, barium, magnesium and calcium) ammonium, and the organic cations such as dibenzylammonium, benzylammonium, 2-hydroxymethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylammonium, dibebenzylethylene-diammonium, and like cations. Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. A preferred cation for a carboxylate anion is the sodium cation.

The compounds of an above Formula can also exist as solvates and hydrates. Thus, these compounds can crystalize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

One or more of the contemplated compounds can be in the biologically active ester form, such as the non-toxic, metabolically-labile ester-form. Such ester forms induce increased blood levels and prolong the efficacy of the corresponding non-esterified forms of the compounds. Ester groups that can be used include the lower alkoxymethyl groups (C_1-C_4 alkoxymethyl) for example, methoxymethyl, ethoxymethyl, isopropoxymethyl and the like; the α-(C_1-C_4) alkoxyethyl groups, for example methoxyethyl, ethoxyethyl, propxyethyl, iso-propoxyethyl, and the like, the 2-oxo-1,3-dioxolen-4-ylmethyl groups such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-phenyl-2-oxo-1,3-dioxolen-4-ylmethyl, and the like, the C_1-C_3 alkylthiomethyl groups, for example methylthio-methyl, ethylthiomethyl, isopropylthiomethyl, and the like, the acyloxymethyl groups, for example pivaloyloxymethyl, pivaloyloxyethyl, α-acetoxymethyl, and the like, the ethoxycarbonyl-1-methyl group, the α-acetoxyethyl, the 3-phthalidyl or 5,6-dimethyl-phtalidyl groups, the 1-(C_1-C_4 alkyloxycarbonyloxy)-ethyl groups such as the 1-(ethoxycarbonyloxy)ethyl group, and the 1-(C_1-C_4 alkylaminocarbonyloxy)ethyl groups such as the 1-methylaminocarbonyloxyethyl group.

As used herein, a chemical or combinatorial "library" is an intentionally created collection of differing molecules that can be prepared by the synthetic means provided below or otherwise herein and screened for biological activity in a variety of

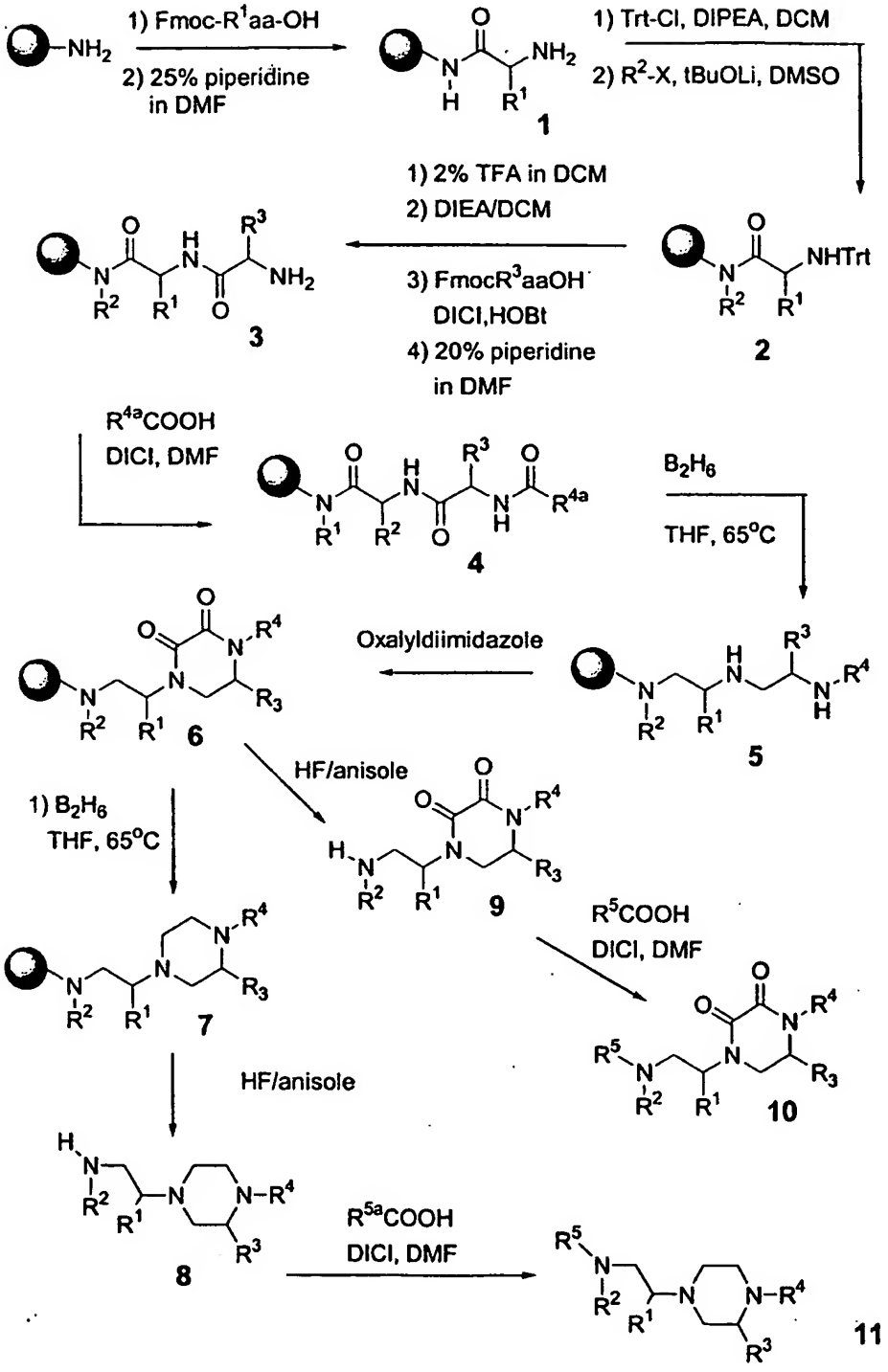
formats (e.g. libraries of soluble molecules). Libraries of compounds attached to resin beads, silica chips or other solid supports). The libraries can be screened in any variety of assays, such as those detailed below as well as others useful for assessing the biological activity of diketopiperazines. The libraries typically contain at least one active compound and are generally prepared in such that the compounds are in equimolar quantities.

Compound and Library Synthesis

As will be described in further detail, illustrative libraries were prepared, two trisubstituted diketopiperazines (one having R^2 as methyl and the other having R^2 as benzyl). The diketopiperazine libraries and compounds of Formula I can be prepared according to the general Reaction Scheme shown in Scheme 1, below, and discussed in greater detail hereinafter.

The compounds and libraries were prepared using solid-phase techniques. The solid-phase resin, here is p-methylbenzhydryl-amine resin (p-MBHA), is indicated in Scheme 1, below, by the large circle and dash. Compound preparation is illustrated first.

Scheme 1


1) Fmoc-R1aa-OH
2) 25% piperidine in DMF
1
1) Trt-Cl, DIPEA, DCM
2) R2-X, tBuOLi, DMSO
2
1) 2% TFA in DCM
2) DIEA/DCM
3) FmocR3aaOH DICI,HOBt
4) 20% piperidine in DMF
3
R4aCOOH
DICI, DMF
4
B2H6
THF, 65°C
5
Oxalyldiimidazole
6
HF/anisole
9
1) B2H6
THF, 65°C
7
R5COOH
DICI, DMF
10
HF/anisole
8
R5aCOOH
DICI, DMF
11

Starting from p-methylbenzhydrylamine (MBHA) resin-bound fluoroenylmethoxycarbonyl amino acid (Fmoc-R^1aa-OH), the Fmoc group was removed using a mixture of piperidine in dimethylformamide (DMF). The resulting amine, compound **1**, was then protected with triphenylmethyl chloride (TrtCl). The secondary amide was then selectively alkylated in the presence of lithium t-butoxide and alkylating reagent, R^2X, in this instance methyl iodide or benzyl bromide to form the resin-bound N-alkylated compound **2**. The Trt group was cleaved with a solution of 2% trifluoroacetic acid (TFA) and a second amino acid (Fmoc-R^3aa-OH) was coupled in presence of diisopropylcarbodiimide and hydroxybenzotriazole from which the Fmoc protecting group was removed to form the resin-bound dipeptide **3**. The resin bound-dipeptide was N-acylated with a wide variety of carboxylic acids (R^{4a}COOH) to form the resin-bound N-acylated dipeptide **4**. Exhaustive reduction of the amide bonds of the resin-bound N-acylated dipeptide **4** was achieved using borane in tetrahydrofuran as described, for instance, in Ostresh et al., *J. Org. Chem.*, 63:8622 (1998) and in Nefzi et al., *Tetrahedron*, 55:335 (1999). The resulting resin-bound polyamine **5** was then treated with oxalyldiimidazole in anhydrous DMF to form resin-bound diketopiperazine **6**. Reaction of resin-bound compound **6** with anhydrous HF and anisole provided a desired diketopiperazine **9**, which could be further N-acylated with a wide variety of carboxylic acids

($R^{5a}COOH$) to provide compound **10**. Further reduction of resin-bound compound **6** with diborane in THF provided corresponding resin-bound piperazine compound **7**. Reaction of compound **7** with anhydrous HF and anisole provided a desired free piperazine compound **8**, which could be further N-acylated with a wide variety of carboxylic acids ($R^{5a}COOH$) as before to provide compound **11**.

Following the strategy described in Scheme 1, with the parallel synthesis approach, commonly referred to as the "T-bag" method [Houghten *et al.*, Nature, 354, 84-86 (1991)], with 29 different amino acids at R^1, 27 different amino acids at R^3 and 40 different carboxylic acids at R^4, 97 different N-benzyl-diketopiperazines, (R^2 = Bzl) and 97 different N-methyl diketopiperazines, (R^2 = Me) were synthesized in which the individual building blocks were varied while fixing the remaining two positions. Those compounds are illustrated as the diketopiperazines in the Table after Example 2.

Modifications occurring to the amino acid side chains during the N-alkylation and reduction steps have been carefully studied. During the N-alkylation with methyl iodide and benzyl bromide, the protected N^{ε}-amine of lysine was alkylated, and the Boc protecting group, when present, was reduced during the reduction step yielding the corresponding N^{ε},N^{ε}-dimethyl and N^{ε}-benzyl, N^{ε}-methyl-polyamines, respectively.

Using the information from these control studies and following the selection of the appropriate compounds for each of the three positions of diversity, N-benzyl (R^2 = Bzl) diketopiperazine and N-methyl (R^2= Me) diketopiperazine libraries were prepared.

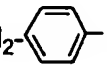
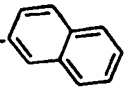
Any variety of amino acids can be used with the present invention as described above to generate a vast array of compounds with different R^1 and R^3 groups. As described in the ensuing Examples, twenty-nine first amino acids were coupled to the resin, which amino acids contain R^1. The twenty nine amino acids included Ala, Phe, Gly, Ile, Leu, Nva, Ser(tBu), Thr(tBu), Val, Tyr(tBu), Nle, Cha, Nal, Phg, Lys (Boc), Met(O), ala, phe, ile, leu, nva, ser(tBu), thr(tBu), val, tyr(tBu), nle, cha, nal, lys(Boc). After the above described N-alkylation, twenty-seven different amino acids were used for the coupling of the second amino acid, thereby providing twenty-seven various R^3 groups. Those twenty seven-amino acids included Ala, Phe, Gly, Ile, Leu, Nva, Ser(tBu), Thr(tBu), Val, Tyr(tBu), Nle, Cha, Nal, Phg, Met(O), ala, phe, ile, leu, nva, ser(tBu), thr(tBu), val, tyr(tBu), nle, cha and nal. Following usual notation, L-amino acids are referred to with an initial capital letter as in Val, whereas D-amino acids are referred to with an initial lower case letter as in ala.

As used herein, abbreviations for the various amino acid side-chain protecting groups are as

follows: "Trt" for trityl, "tBu" for tert-butyl, "Boc" for tert-butoxycarbonyl and "BrZ" for 2-bromobenzyloxycarbonyl.

As can be seen from the amino acid side chains exemplified above, it should be appreciated from the above-described embodiments of R^1 and R^3, as well as from the described reaction scheme, that some of the amino acid side chains are modified during the synthesis. For instance some of the R^1 amino acid side chains are modified by the N-alkylation and/or the reduction steps. Similarly, certain R^3 groups are modified by the reduction procedures. Accordingly, the twenty-nine preferred embodiments of R^1 and the twenty-seven of R^3 are described above and below, except in Table 1, in their modified form. A specific example of a modified lysine side is provided above. Similarly, certain R^4 groups can be modified by the reduction procedure, as is well known.

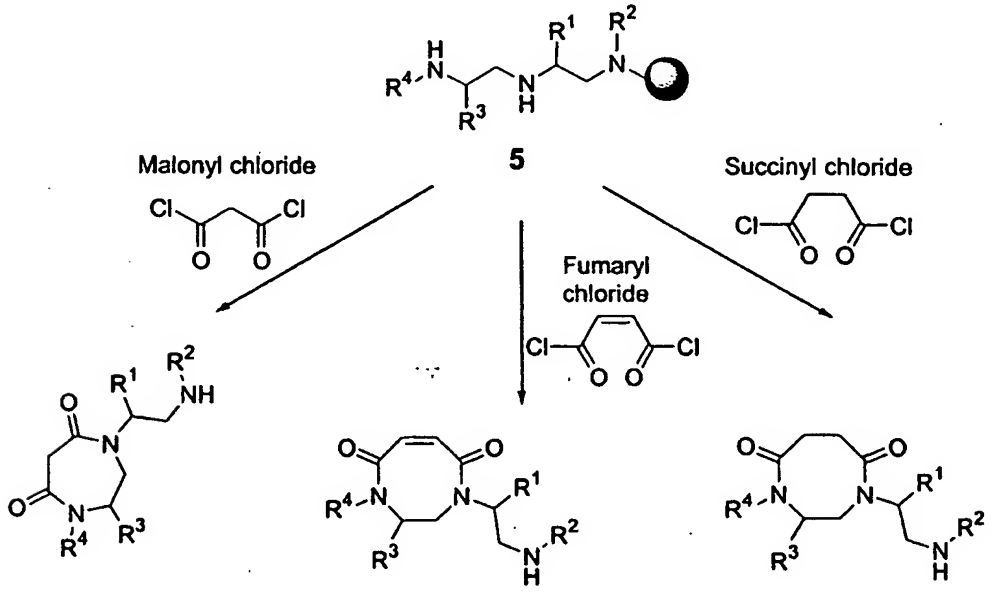
Table 1

Amino acid name		Side chain R
Full	3-letter code	(For R^1 and R^3)
Glycine	Gly	~H
Alanine	Ala	~CH_3
Valine	Val	~$CH(CH_3)_2$
Leucine	Leu	~CH_2-$CH(CH_3)_2$
Isoleucine	Ile	~$CH(CH_3)CH_2CH_3$
Lysine	Lys	~$(CH_2)_4$-NH_2
Serine	Ser	~CH_2-OH
Threonine	Thr	~$CH(CH_3)$-OH
Phenylalanine	Phe	~CH_2- 
Tyrosine	Tyr	~CH_2-  -OH
Norvaline	Nva	~$(CH_2)_2$-CH_3
Norleucine	Nle	~$(CH_2)_3$-CH_3
Naphthylalanine	Nal	~CH_2- 
Cyclohexylalanine	Cha	~CH_2- 
Methionine	Met	~CH_2-CH_2-S-CH_3
Phenylglycine	Phg	~ 

A variety of carboxylic acids ($R^{4a}COOH$ and $R^{5a}COOH$) can be used in the acylation steps of reaction Scheme 1, thereby providing a wide array of substituents at the R^4 and R^5 positions and substituentds of an illustrative diketopierazine. Forty carboxylic acids were used in preparing the diketopiperazine compounds and libraries. Those syntheses were carried out using the following carboxylic acids: 1-phenyl-1-cyclopropane carboxylic acid, m-tolylacetic acid, 3-fluorophenyl-acetic acid, (α,α,α)–trifluoro-m-tolylacetic acid, p-tolylacetic acid, 3-methoxyphenylacetic acid, 4-methoxyphenyl-acetic acid, 4-ethoxyphenylacetic acid, 4-isobutyl-α-methylphenylacetic acid, 3,4-dichloro-phenylacetic acid, 3,5-bis(trifluoromethyl)phenylacetic acid, phenylacetic acid, hydrocinnamic acid, 4-phenyl-butyric acid, butyric acid, heptanoic acid, isobutyric acid, isovaleric acid, 4-methylvaleric acid, trimethylacetic acid, tert-butylacetic acid, cyclohexanecarboxylic acid, cyclohexylacetic acid, cyclohexanebutyric acid, cycloheptanecarboxylic acid, acetic acid, cyclobutanecarboxylic acid, cyclopentanecarboxylic acid, cyclohexanepropionic acid, 4-methyl-1-cyclohexanecarboxylic acid, 4-tert-butyl-cyclohexanecarboxylic acid, 1-adamantaneacetic acid, 3,3-diphenylpropionic acid, dicyclohexylacetic acid, indole-3-acetic acid, 1-naphthylacetic acid, 3-(3,4,5)-trimethoxyphenylpropionic acid, 2-norbornaneacetic acid, cyclopentylacetic acid, 2-ethylbutyric acid.

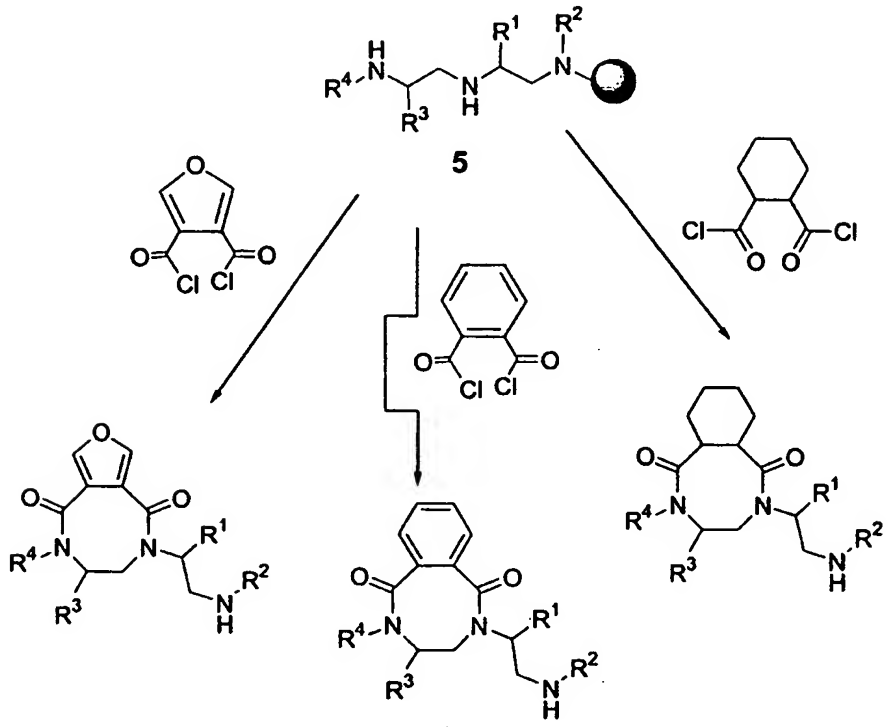
The synthesis of 1,6-diketo-(2-substituted or 2,3-disubstituted)-(5-aminoethyl)-2,5-diazacyclic compounds and the corresponding (1-substituted or 1,2-disubstituted)-(4-aminoethyl)-(1,4-diazacyclic compounds having 7- or 8-atoms in the cyclic ring or an unsaturated bond between the two carbonyl groups can be carried out in a similar manner to that shown in Scheme 1 by reacting a longer activated diacid such as a diacid halide like a diacid chloride or diimidazole compound with resin-bound compound 5. A tertiary amine such as diisopropylethylamine is typically also present when a diacid chloride or similar compound is used in these syntheses. Exemplary reactions are shown in Scheme 2, below, wherein only the ring-forming step is shown

Scheme 2



Bi- and tricyclic compounds can be prepared using the same general synthetic steps, but using a cyclic activated α,β-diacid as is illustrated in Scheme 3, below.

Scheme 3



It is to be understood that the 1,4-diazacyclic compounds corresponding to those shown in Schemes 2 and 3 are prepared and further reacted in the same manner as are the 1,4-diazacyclic compounds of Scheme 1.

Compounds and libraries containing a single amido carbonyl group can be prepared by several well-known synthetic methods. For example, a substituted

or unsubstituted acryloyl halide can be reacted using a Michael addition to one amine of compound 5 and the acid halide used to form the amide bond with the second amine.

The nonsupport-bound library mixtures were screened in solution in radio-receptor inhibition assays described in detail below. Deconvolution of highly active mixtures can then be carried out by iterative, or positional scanning methods. These techniques, the iterative approach or the positional scanning approach, can be utilized for finding other active compounds within the libraries of the present invention using any one of the below-described assays or others well known in the art.

The iterative approach is well-known and is set forth in general in Houghten *et al.*, Nature, 354, 84-86 (1991) and Dooley *et al.*, Science, 266, 2019-2022 (1994), both of which are incorporated herein by reference. In the iterative approach, for example, sub-libraries of a molecule having three variable groups are made wherein the first variable is defined. Each of the compounds with the defined variable group is reacted with all of the other possibilities at the other two variable groups. These sub-libraries are each assayed to define the identity of the second variable in the sub-library having the highest activity in the screen of choice. A new sub-library with the first two variable positions defined is reacted again with all the other possibilities at the remaining undefined variable position. As before, the identity of the third variable position in the sub-library having the

highest activity is determined. If more variables exist, this process is repeated for all variables, yielding the compound with each variable contributing to the highest desired activity in the screening process. Promising compounds from this process can then be synthesized on larger scale in traditional single-compound synthetic methods for further biological investigation.

The positional-scanning approach has been described for various libraries as described, for example, in R. Houghten *et al.* PCT/US91/08694 and U.S. Patent 5,556,762, both of which are incorporated herein by reference. The positional scanning approach is used as described below in the preparation and screening of the libraries. In the positional scanning approach sublibraries are made defining only one variable with each set of sublibraries- and all possible sublibraries with each single variable defined (and all other possibilities at all of the other variable positions) is made and tested. From the instant description one skilled in the art can synthesize libraries wherein 2 fixed positions are defined at a time. From the assaying of each single-variable defined library, the optimum substituent at that position is determined, pointing to the optimum or at least a series of compounds having a maximum of the desired biological activity. Thus, the number of sublibraries for compounds with a single position defined is the number of different substituents desired at that position, and the number of all the compounds in each sublibrary is the

product of the number of substituents at each of the other variables.

As pharmaceutical compositions for treating infections, pain, or other indications known to be treatable by a contemplated diketopiperazine or other contemplated compound, a compound of the present invention is generally in a pharmaceutical composition so as to be administered to a subject in need of the medication at dosage levels of about 0.7 to about 7000 mg per day, and preferably about 1 to about 500 mg per day, for a normal human adult of approximately 70 kg of body weight, this translates into a dosage of about 0.01 to about 100 mg/kg of body weight per day. The specific dosages employed, however, can be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

For preparing pharmaceutical compositions containing compounds of the invention, inert, pharmaceutically acceptable carriers are used. The pharmaceutical carrier can be either solid or liquid. Solid form preparations include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances that can also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders,

or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is generally a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing pharmaceutical composition in the form of suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient. Suitable carriers include, for example, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter and the like.

The pharmaceutical compositions can include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid pharmaceutical compositions include, for example, solutions suitable for oral or parenteral administration, or suspensions, and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol are examples of liquid compositions suitable for parenteral administration.

Sterile solutions can be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

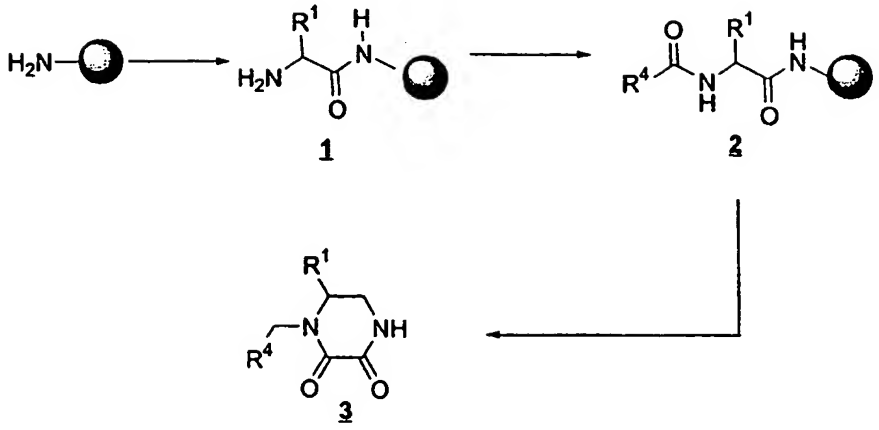
Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical composition is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active urea. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Example 1: Typical Procedure for the Individual Synthesis of 4,5-disubstituted-2,3-diketopiperazines

The synthetic route followed in these preparations is illustrated in Scheme 4, below, whose reactants are discussed in the text that follows.

Scheme 4



1) Amino acid coupling and acylation: 100 mg p-methylbenzydrylamine (MBHA) resin (1.0 meq/g, 100-200 mesh) was contained within a sealed polypropylene mesh packet [Houghten, R.A., *Proc. Natl. Acad .Sci. USA* 1985, 82, 5131]. Reactions were carried out in 10 ml polyethylene bottles. Following neutralization with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM), the resin was washed with DCM. The first amino acid (Fmoc-R^1aa-OH, 6 eq) was coupled using the conventional reagents hydroxybenzotriazole (HOBt, 6 eq) and diisopropylcarbodiimide (DIC, 6 eq) in anhydrius DMF for 60 minutes.

2) Following removal of the protecting group with 25% piperidine in DMF (2 times, 2 x 10 minutes) and wash with DMF (8 times), the amino acid was N-acylated with a carboxylic acid (10 eq) in the presence of DIC (10 eq) and HOBt (10 eq) overnight (about 18 hours) in anhydrous DMF.

3) Exhaustive reduction of the amide groups: The reduction was performed in 50 ml Kimax™ tubes under nitrogen. Boric acid (40x) and trimethyl borate (40x) were added, followed by 1M BH_3-THF (40x). The tubes were heated at 65°C for 72 hours, followed by quenching with MeOH. The resin was then washed with methanol (2 times) and the borane was disproportionated by treatment with piperidine at 65°C overnight (about 18 hours). The resin was then washed with methanol (2 times) and DMF (6 times) and dried.

4) Disubstituted diketopiperazine formation: The cyclization occurred following treatment of the reduced acylated amino acid overnight (about 18 hours) with oxalyldiimidazole (15 x) in DMF anhydrous. Following cleavage from the resin with anhydrous HF in the presence of anisole at 0°C for 6 hours, the desired product was extracted with acetonitrile/water (50:50) and lyophilized.

Product Data:

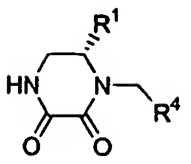
3a: ^{1}H NMR (500 MHZ, DMSO-d_6) δ. 8.43 (d, J= 4.53 Hz, 1H), 7.32-6.66 (m, 9H), 3.88 (m, 1H), 3.76 (m, 1H), 3.23 (dd, J= 13.07, J= 2.43 Hz), 2.89 (m, 1H), 2.88 (m, 2H), 2.82 (m, 2H), 2.63 (dd, J= 13.34, J= 9.51 Hz, 1H). ^{13}C NMR (125 MHZ, DMSO-d_6): 157.48, 157.05, 156.05, 138.89, 130.16, 128.76, 128.37, 127.32, 126.32, 115,28, 56.98, 54.93, 47.52. ES-MS calcd for $C_{19}H_{20}N_2O_3$: 324.37, found: 325.40 (MH^+).

3f: ^{1}H NMR (500 MHZ, DMSO-d_6) δ. 8.45 (d, J= 3.80 Hz, 1H), 7.34-7.23 (m, 5H), 3.72 (m, 1H), 3.64 (dd, J=

13.34, J= 6.91 Hz, 1H), 3.45 (dd, J= 13.21, J= 3.32 Hz), 2.99 (dd, J= 13.35, J= 5.10 Hz, 1H), 2.95 (dd, J= 14.45, J= 5.48 Hz, 1H), 2.88 (dd, J= 13.56, J= 6.92 Hz, 1H), 2.81 (dd, J= 13.10, J= 9.76 Hz, 1H), 1.08 (t, J= 6.94 Hz, 3H). ^{13}C NMR (125 MHZ, DMSO-d_6):157.61, 156.82, 137.44, 129.29, 128.53, 126.68, 55.81, 40.57, 40.20, 36.78, 13.00. ES-MS calcd for $C_{13}H_{16}N_2O_2$: 232.28, found: 233.20 (MH^+).

31: ^{1}H NMR (500 MHZ, DMSO-d_6) δ. 8.47 (d, J= 4.17 Hz, 1H), 3.62 (m, 1H), 3.61 (m, 1H), 3.53, dd, J= 13.45, J= 7.86 Hz, 1H), 3.06 (m, 1H), 2.70 (dd, J= 13.00, J= 7.26 Hz, 1H), 1.93 (m, 1H), 1.22 (d, J= 7.09 Hz, 3H), 0.88 (d, J= 6.73 Hz, 3H), 0.82 (d, J= 6.73 Hz, 3H). ^{13}C NMR (125 MHZ, DMSO-d_6):157.50, 157.44, 51.68, 50.63, 43.17, 26.59, 19.95, 19.90, 16.75. ES-MS calcd for $C_9H_{16}N_2O_2$: 184.24, found: 185.10 (MH^+).

3r: ^{1}H NMR (500 MHZ, DMSO-d_6) δ. 8.34 (d, J= 3.98 Hz, 1H), 3.81 (m, 1H), 3.46 (m, 1H), 3.28 (m, 2H), 2.89 (m, 1H), 1.96 (m, 1H), 1.09 (t, J= 6.91 Hz, 1H), 0.96 (d, J= 6.73 Hz, 3H), 0.88 (d, J= 6.73 Hz, 3H). ^{13}C NMR (125 MHZ, DMSO-d_6):157.50, 157.44, 51.68, 50.63, 43.17, 26.59, 19.95, 19.90, 16.75. ES-MS calcd for $C_9H_{16}N_2O_2$: 184.24, found: 185.20 (MH^+).



3

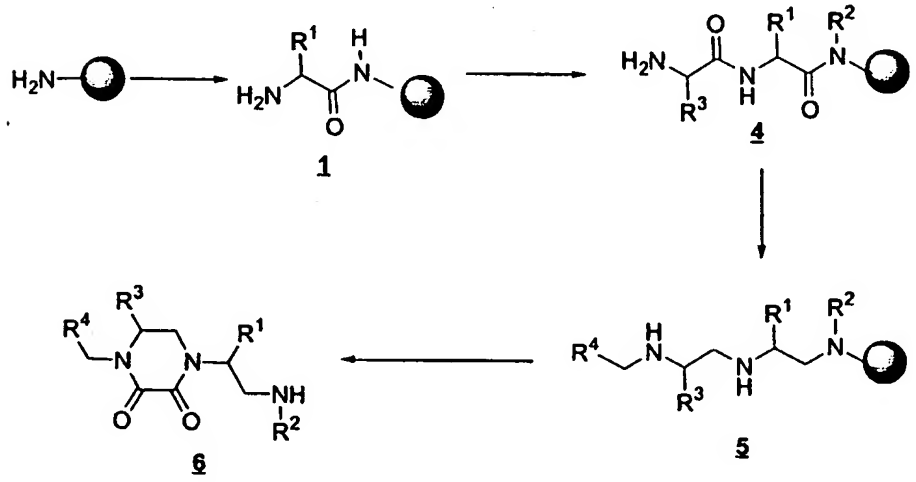
Entry	R^1	R^4	MW expected	MW found
3a	CH_2-C_6H_4-OH*	CH_2Ph	324.37	325.4 (MH^+)
3b	CH_2-C_6H_4-OH	CH_3	248.28	249.2 (MH^+)
3c	CH_2-C_6H_4-OH	CH_2-C_5H_{11}	316.39	317.3 (MH^+)
3d	CH_2-C_6H_4-OH	$CH(CH_3)_2$	276.33	277.2 (MH^+)
3e	CH_2Ph*	CH_2Ph	308.37	309.3 (MH^+)
3f	CH_2Ph	CH_3	232.28	233.2 (MH^+)
3g	CH_2Ph	CH_2-C_5H_{11}	300.40	301.2 (MH^+)
3h	CH_2Ph	$CH(CH_3)_2$	260.33	261.2 (MH^+)
3i	CH_3	CH_2Ph	232.28	233.2 (MH^+)
3j	CH_3	CH_3	156.18	157.2 (MH^+)
3k	CH_3	CH_2-C_5H_{11}	224.30	225.2 (MH^+)
3l	CH_3	$CH(CH_3)_2$	184.24	185.1 (MH^+)
3m	CH_2OH	CH_2Ph	248.28	249.9 (MH^+)
3n	CH_2OH	CH_3	172.18	173.2 (MH^+)
3o	CH_2OH	CH_2-C_5H_{11}	240.30	241.2 (MH^+)
3p	CH_2OH	$CH(CH_3)_2$	200.24	201.9 (MH^+)
3q	$CH(CH_3)_2$	CH_2Ph	260.33	261.2 (MH^+)
3r	$CH(CH_3)_2$	CH_3	184.24	185.2 (MH^+)
3s	$CH(CH_3)_2$	CH_2-C_5H_{11}	252.35	253.2 (MH^+)
3t	$CH(CH_3)_2$	$CH(CH_3)_2$	212.29	213.2 (MH^+)

* C_6H_4 is phenyl and Ph is phenyl.

Example 2: Typical Procedure for the Individual synthesis of 1,4,5-Trisubstituted-2,3-diketopiperazines

The compounds of this example were prepared following the general reaction pathway shown in Scheme 5, below, wherein the reactants are discussed in the following text.

Scheme 5



1) Amino acid coupling and selective amide N-alkylation: The first amino acid was coupled in the same conditions as described before. Following removal of the protecting group with 25% piperidine in DMF (2 times, 2 x 10 minutes) and washing with DMF (8 times), the mesh packet was shaken overnight (about 18 hours) in a solution of trityl chloride in DCM/DMF (9:1) in the presence of DIEA. Completeness of the trityl coupling was verified using the bromophenol blue color test [Krchák, V. et al., *Coll. Czech. Chem. Comm*, 1988, 53, 2542]. N-alkylation was performed by treatment of the resin packet with 1 M lithium t-butoxide in THF (20 eq) during 10 minutes at room temperature. Excess base was removed by cannulation, followed by addition of the individual

alkylating agent (20 eq) in anhydrous DMSO. The solution was vigorously shaken for 2 hours at room temperature.

2) N-acylated dipeptide: Upon removal of the trityl from the α-amino group with 2% TFA in DCM (2 x 10 min), the resin packet was washed, neutralized with a solution of 5% DIEA in DCM, and the second amino acid (Fmoc-R^3aa-OH) coupled in the same conditions as described before. Following removal of the Fmoc group, the dipeptide was N-acylated with a carboxylic acid (10 eq) in the presence of DIC (10 eq) and HOBt (10 eq) in anhydrous DMF.

3) Exhaustive reduction of the amide groups: The reduction was performed in the same conditions as described before.

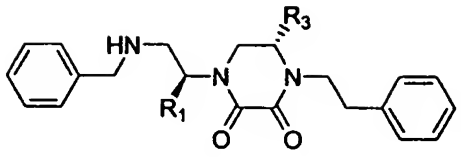
4) Trisubstituted diketopiperazine formation: The cyclization occurred following treatment of the reduced acylated dipeptide overnight (about 18 hours) with oxalyldiimidazole (15 x) in DMF anhydrous. Following cleavage from the resin with anhydrous HF in the presence of anisole at 0°C for 6 hours [Houghten, R.A. et al., *Int. J. Pep. Pro. Res.*, 1986, 27, 6763], the desired product was extracted with acetonitrile/water (50:50) and lyophilized.

Product Data:

6i: ^{1}H NMR (500 MHZ, DMSO-d_6) δ 7.13-7.6 (m, 20 H), 4.37 (m, 1H), 4.15-4.23 (m, 2H), 3.67-3.83 (m, 8H), 3.35 (m, 1H), 2.94-3.09 (m, 4H), 2.67-2.84 (m, 4H), 1.58 (m, 2H), 1.16 (m, 1H). ^{13}C NMR (125 MHZ, DMSO-

d_6): 157.58, 155.97, 138.69, 137.53, 131.41, 131.15, 130.21, 129.89, 129.62, 129.17, 129.04, 128.91, 128.73, 128.68, 128.39, 126.79, 126.36, 58.39, 55.32, 54.34, 50.62, 47.94, 47.65, 37.16, 33.00, 28.42, 22.92. ES-MS calcd for $C_{40}H_{48}N_4O_2$: 616.34, found: 617.60 (MH^+).

6e: ^1H NMR (500 MHZ, DMSO-d_6) δ 7.24-7.36 (m, 15H), 5.13 (m, 1H), 4.57 (d, J= 14.5 Hz, 1H), 4.46 (d, J= 14.5 Hz, 1H), 4.12 (dd, J= 8.7, 14.8 Hz, 1H), 3.92 (m, 1H), 3.51 (m, 2H), 3.18-3,26 (m, 5H), 3.08 (dd, J= 3.8, 14.8 Hz, 1H), 2.88 (m, 3H). ^{13}C NMR (125 MHZ, DMSO-d_6): 158.47, 156.14, 136.92, 136.13, 129.10, 128.72, 128.64, 128.55, 128.23, 127.56, 127.08, 126.88, 60.06, 56.18, 54.57, 49.92, 46.20, 44.96, 44.72, 42.50, 36.22, 34.57, 31.73. ES-MS calcd for $C_{29}H_{33}N_3O_3$: 471.25, found: 472.2 (MH^+).



6

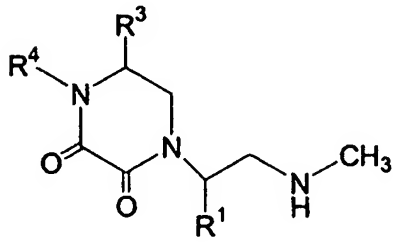
Entry	R_1	R_3	MW expected	MW found
6a	CH_2Ph*	CH_2Ph	531.29	532.2 (MH^+)
6b	CH_2Ph	$CH(CH_3)_2$	483.29	484.3 (MH^+)
6c	$CH(CH_3)CH_2CH_3$	CH_2Ph	497.30	498.3 (MH^+)
6d	$CH(CH_3)CH_2CH_3$	$CH(CH_3)_2$	449.30	450.3 (MH^+)
6e	CH_2OH	CH_2Ph	471.25	472.2 (MH^+)
6f	CH_2OH	$CH(CH_3)_2$	423.25	424.2 (MH^+)
6g	CH_3	CH_2Ph	455.26	456.3 (MH^+)
6h	CH_3	$CH(CH_3)_2$	407.26	408.3 (MH^+)
6i	$(CH_2)_4N(CH_3)CH_2Ph$	CH_2Ph	616.38	617.6 (MH^+)
6j	$(CH_2)_4N(CH_3)CH_2Ph$	$CH(CH_3)_2$	568.38	569.5 (MH^+)

*Ph is monosubstituted phenyl.

Lists of individual N-benzyl and N-methyl compounds prepared as discussed in this example is provided below in Tables 2 and 3. The compounds are listed by preparation number (Prep) followed by the amino acid or carboxylic acid used to provide R^1, R^3 and R^4.

Table 2

N-Benzyl and N-Methyl
-1,4,5-trisubstituted
-2,3-diketopiperazines



Prep	R^1	R^3	R^4
1	Fmoc-Ala	Fmoc-Phe	Phenylacetic Acid
2	Fmoc-Phe	Fmoc-Phe	Phenylacetic Acid
3	Fmoc-Gly	Fmoc-Phe	Phenylacetic Acid
4	Fmoc-Ile	Fmoc-Phe	Phenylacetic Acid
5	Fmoc-Lys(Boc)	Fmoc-Phe	Phenylacetic Acid
6	Fmoc-Leu	Fmoc-Phe	Phenylacetic Acid
7	Fmoc-Met(O)	Fmoc-Phe	Phenylacetic Acid
8	Fmoc-Ser(tBut)	Fmoc-Phe	Phenylacetic Acid
9	Fmoc-Thr(tBut)	Fmoc-Phe	Phenylacetic Acid
10	Fmoc-Val	Fmoc-Phe	Phenylacetic Acid
11	Fmoc-Tyr(tBut)	Fmoc-Phe	Phenylacetic Acid
12	Fmoc-ala	Fmoc-Phe	Phenylacetic Acid
13	Fmoc-phe	Fmoc-Phe	Phenylacetic Acid
14	Fmoc-ile	Fmoc-Phe	Phenylacetic Acid
15	Fmoc-lys(Boc)	Fmoc-Phe	Phenylacetic Acid
16	Fmoc-leu	Fmoc-Phe	Phenylacetic Acid
17	Fmoc-ser(tBut)	Fmoc-Phe	Phenylacetic Acid
18	Fmoc-thr(tBut)	Fmoc-Phe	Phenylacetic Acid
19	Fmoc-val	Fmoc-Phe	Phenylacetic Acid
20	Fmoc-tyr(tBut)	Fmoc-Phe	Phenylacetic Acid
21	Fmoc-Nle	Fmoc-Phe	Phenylacetic Acid
22	Fmoc-nle	Fmoc-Phe	Phenylacetic Acid
23	Fmoc-Nva	Fmoc-Phe	Phenylacetic Acid
24	Fmoc-nva	Fmoc-Phe	Phenylacetic Acid
25	Fmoc-NapAla	Fmoc-Phe	Phenylacetic Acid

26	Fmoc-napala	Fmoc-Phe	Phenylacetic Acid
27	Fmoc-Phg	Fmoc-Phe	Phenylacetic Acid
28	Fmoc-ChAla	Fmoc-Phe	Phenylacetic Acid
29	Fmoc-chala	Fmoc-Phe	Phenylacetic Acid
30	Fmoc-Phe	Fmoc-Ala	Phenylacetic Acid
31	Fmoc-Phe	Fmoc-Phe	Phenylacetic Acid
32	Fmoc-Phe	Fmoc-Gly	Phenylacetic Acid
33	Fmoc-Phe	Fmoc-Ile	Phenylacetic Acid
34	Fmoc-Phe	Fmoc-Leu	Phenylacetic Acid
35	Fmoc-Phe	Fmoc-Met(O)	Phenylacetic Acid
36	Fmoc-Phe	Fmoc-Ser(tBut)	Phenylacetic Acid
37	Fmoc-Phe	Fmoc-Thr(tBut)	Phenylacetic Acid
38	Fmoc-Phe	Fmoc-Val	Phenylacetic Acid
39	Fmoc-Phe	Fmoc-Tyr(tBut)	Phenylacetic Acid
40	Fmoc-Phe	Fmoc-ala	Phenylacetic Acid
41	Fmoc-Phe	Fmoc-phe	Phenylacetic Acid
42	Fmoc-Phe	Fmoc-ile	Phenylacetic Acid
43	Fmoc-Phe	Fmoc-leu	Phenylacetic Acid
44	Fmoc-Phe	Fmoc-ser(tBut)	Phenylacetic Acid
45	Fmoc-Phe	Fmoc-thr(tBut)	Phenylacetic Acid
46	Fmoc-Phe	Fmoc-val	Phenylacetic Acid
47	Fmoc-Phe	Fmoc-tyr(tBut)	Phenylacetic Acid
48	Fmoc-Phe	Fmoc-Nle	Phenylacetic Acid
49	Fmoc-Phe	Fmoc-nle	Phenylacetic Acid
50	Fmoc-Phe	Fmoc-Nva	Phenylacetic Acid
51	Fmoc-Phe	Fmoc-nva	Phenylacetic Acid
52	Fmoc-Phe	Fmoc-NapAla	Phenylacetic Acid
53	Fmoc-Phe	Fmoc-napAla	Phenylacetic Acid
54	Fmoc-Phe	Fmoc-Phg	Phenylacetic Acid
55	Fmoc-Phe	Fmoc-ChAla	Phenylacetic Acid
56	Fmoc-Phe	Fmoc-chala	Phenylacetic Acid
57	Fmoc-Phe	Fmoc-Phe	1-Phenyl-1-cyclopropane-carboxylic Acid
58	Fmoc-Phe	Fmoc-Phe	m-Tolylacetic Acid
59	Fmoc-Phe	Fmoc-Phe	3-Fluorophenyl-acetic Acid
60	Fmoc-Phe	Fmoc-Phe	(α,α,α-Trifluoro-m-tolyl)acetic acid
61	Fmoc-Phe	Fmoc-Phe	p-Tolylacetic Acid

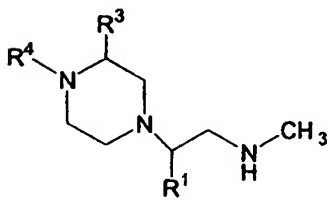
62	Fmoc-Phe	Fmoc-Phe	3-Methoxyphenyl-acetic Acid
63	Fmoc-Phe	Fmoc-Phe	4-Methoxyphenyl-acetic Acid
64	Fmoc-Phe	Fmoc-Phe	4-Ethoxyphenyl-acetic Acid
65	Fmoc-Phe	Fmoc-Phe	4-Isobutyl-α-Methylphenyl-acetic Acid
66	Fmoc-Phe	Fmoc-Phe	3,4-Dichlorophenyl-acetic Acid
67	Fmoc-Phe	Fmoc-Phe	3,5-Bis(trifluoromethyl)-phenylacetic Acid
68	Fmoc-Phe	Fmoc-Phe	Phenylacetic Acid
69	Fmoc-Phe	Fmoc-Phe	Hydrocinnamic Acid
70	Fmoc-Phe	Fmoc-Phe	4-Phenylbutyric Acid
71	Fmoc-Phe	Fmoc-Phe	Butyric Acid
72	Fmoc-Phe	Fmoc-Phe	Heptanoic Acid
73	Fmoc-Phe	Fmoc-Phe	Isobutyric Acid
74	Fmoc-Phe	Fmoc-Phe	Isovaleric Acid
75	Fmoc-Phe	Fmoc-Phe	4-Methylvaleric Acid
76	Fmoc-Phe	Fmoc-Phe	Trimethylacetic Acid
77	Fmoc-Phe	Fmoc-Phe	tert-Butylacetic Acid
78	Fmoc-Phe	Fmoc-Phe	Cyclohexane-carboxylic Acid
79	Fmoc-Phe	Fmoc-Phe	Cyclohexyl-acetic Acid
80	Fmoc-Phe	Fmoc-Phe	Cyclohexane-butyric Acid
81	Fmoc-Phe	Fmoc-Phe	Cycloheptane-carboxylic Acid
82	Fmoc-Phe	Fmoc-Phe	Acetic Acid
83	Fmoc-Phe	Fmoc-Phe	Cyclobutane-carboxylic Acid
84	Fmoc-Phe	Fmoc-Phe	Cyclopentane-carboxylic Acid

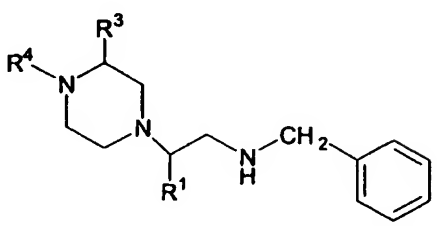
85	Fmoc-Phe	Fmoc-Phe	Cyclohexane-propionic Acid
86	Fmoc-Phe	Fmoc-Phe	4-Methyl-1-cyclohexane-carboxylic Acid
87	Fmoc-Phe	Fmoc-Phe	4-tert-Butyl-cyclohexane-carboxylic Acid
88	Fmoc-Phe	Fmoc-Phe	1-Adamantane-acetic Acid
89	Fmoc-Phe	Fmoc-Phe	3,3-Diphenyl-propionic Acid
90	Fmoc-Phe	Fmoc-Phe	Dicyclohexy-lacetic Acid
91	Fmoc-Phe	Fmoc-Phe	Indole-3-acetic Acid
92	Fmoc-Phe	Fmoc-Phe	1-Naphthylacetic Acid
93	Fmoc-Phe	Fmoc-Phe	3-(3,4,5-Trimethoxy-phenyl)propionic Acid
94	Fmoc-Phe	Fmoc-Phe	2-Norbornane acetic Acid
95	Fmoc-Phe	Fmoc-Phe	Cyclopentyl-acetic Acid
96	Fmoc-Phe	Fmoc-Phe	2-Ethylbutyric acid

Table 3

Individual N-Methyl- and N-Benzyl-1,4,5-trisubstituted piperazine

Compounds Synthesized





Prep	R^1	R^3	R^4
01	Fmoc-Ala	Fmoc-Phe	Phenylacetic Acid
02	Fmoc -Phe	Fmoc-Phe	Phenylacetic Acid
03	Fmoc-Gly	Fmoc-Phe	Phenylacetic Acid
04	Fmoc-Ile	Fmoc-Phe	Phenylacetic Acid
05	Fmoc-Lys(Boc)	Fmoc-Phe	Phenylacetic Acid
06	Fmoc-Leu	Fmoc-Phe	Phenylacetic Acid
07	Fmoc-Met(O)	Fmoc-Phe	Phenylacetic Acid
08	Fmoc-Ser(tBut)	Fmoc-Phe	Phenylacetic Acid
09	Fmoc-Thr(tBut)	Fmoc-Phe	Phenylacetic Acid
10	Fmoc-Val	Fmoc-Phe	Phenylacetic Acid
11	Fmoc-Tyr(tBut)	Fmoc-Phe	Phenylacetic Acid
12	Fmoc-ala	Fmoc-Phe	Phenylacetic Acid
13	Fmoc-phe	Fmoc-Phe	Phenylacetic Acid
14	Fmoc-ile	Fmoc-Phe	Phenylacetic Acid
15	Fmoc-lys(Boc)	Fmoc-Phe	Phenylacetic Acid
16	Fmoc-leu	Fmoc-Phe	Phenylacetic Acid
17	Fmoc-ser(tBut)	Fmoc-Phe	Phenylacetic Acid
18	Fmoc-thr(tBut)	Fmoc-Phe	Phenylacetic Acid
19	Fmoc-val	Fmoc-Phe	Phenylacetic Acid
20	Fmoc-tyr(tBut)	Fmoc-Phe	Phenylacetic Acid
21	Fmoc-Nle	Fmoc-Phe	Phenylacetic Acid
22	Fmoc-nle	Fmoc-Phe	Phenylacetic Acid
23	Fmoc-Nva	Fmoc-Phe	Phenylacetic Acid
24	Fmoc-nva	Fmoc-Phe	Phenylacetic Acid
25	Fmoc-NapAla	Fmoc-Phe	Phenylacetic Acid
26	Fmoc-napala	Fmoc-Phe	Phenylacetic Acid
27	Fmoc-Phg	Fmoc-Phe	Phenylacetic Acid
28	Fmoc-ChAla	Fmoc-Phe	Phenylacetic Acid
29	Fmoc-chala	Fmoc-Phe	Phenylacetic Acid
30	Fmoc-Phe	Fmoc-Ala	Phenylacetic Acid
31	Fmoc-Phe	Fmoc -Phe	Phenylacetic Acid
32	Fmoc-Phe	Fmoc-Gly	Phenylacetic Acid
33	Fmoc-Phe	Fmoc-Ile	Phenylacetic Acid
34	Fmoc-Phe	Fmoc-Leu	Phenylacetic Acid
35	Fmoc-Phe	Fmoc-Met(O)	Phenylacetic Acid
36	Fmoc-Phe	Fmoc-Ser(tBut)	Phenylacetic Acid
37	Fmoc-Phe	Fmoc-Thr(tBut)	Phenylacetic Acid
38	Fmoc-Phe	Fmoc-Val	Phenylacetic Acid

39	Fmoc-Phe	Fmoc-Tyr(tBut)	Phenylacetic Acid
40	Fmoc-Phe	Fmoc-ala	Phenylacetic Acid
41	Fmoc-Phe	Fmoc-phe	Phenylacetic Acid
42	Fmoc-Phe	Fmoc-ile	Phenylacetic Acid
43	Fmoc-Phe	Fmoc-leu	Phenylacetic Acid
44	Fmoc-Phe	Fmoc-ser(tBut)	Phenylacetic Acid
45	Fmoc-Phe	Fmoc-thr(tBut)	Phenylacetic Acid
46	Fmoc-Phe	Fmoc-val	Phenylacetic Acid
47	Fmoc-Phe	Fmoc-tyr(tBut)	Phenylacetic Acid
48	Fmoc-Phe	Fmoc-Nle	Phenylacetic Acid
49	Fmoc-Phe	Fmoc-nle	Phenylacetic Acid
50	Fmoc-Phe	Fmoc-Nva	Phenylacetic Acid
51	Fmoc-Phe	Fmoc-nva	Phenylacetic Acid
52	Fmoc-Phe	Fmoc-NapAla	Phenylacetic Acid
53	Fmoc-Phe	Fmoc-napala	Phenylacetic Acid
54	Fmoc-Phe	Fmoc-Phg	Phenylacetic Acid
55	Fmoc-Phe	Fmoc-ChAla	Phenylacetic Acid
56	Fmoc-Phe	Fmoc-chala	Phenylacetic Acid
57	Fmoc-Phe	Fmoc-Phe	1-Phenyl-1-cyclopropane-carboxylic Acid
58	Fmoc-Phe	Fmoc-Phe	m-Tolylacetic Acid
59	Fmoc-Phe	Fmoc-Phe	3-Fluorophenylacetic Acid
60	Fmoc-Phe	Fmoc-Phe	(α,α,α-Trifluoro-m-tolyl)-acetic Acid
61	Fmoc-Phe	Fmoc-Phe	p-Tolylacetic Acid
62	Fmoc-Phe	Fmoc-Phe	3-Methoxyphenylacetic Acid
63	Fmoc-Phe	Fmoc-Phe	4-Methoxyphenylacetic Acid
64	Fmoc-Phe	Fmoc-Phe	4-Ethoxyphenylacetic Acid
65	Fmoc-Phe	Fmoc-Phe	4-Isobutyl-α-methyl-phenylacetic Acid
66	Fmoc-Phe	Fmoc-Phe	3,4-Dichlorophenyl-acetic Acid
67	Fmoc-Phe	Fmoc-Phe	3,5-Bis(trifluoro-methyl)phenylacetic Acid
68	Fmoc-Phe	Fmoc-Phe	Phenylacetic Acid
69	Fmoc-Phe	Fmoc-Phe	Hydrocinnamic Acid
70	Fmoc-Phe	Fmoc-Phe	4-Phenylbutyric Acid
71	Fmoc-Phe	Fmoc-Phe	Butyric Acid

72	Fmoc-Phe	Fmoc-Phe	Heptanoic Acid
73	Fmoc-Phe	Fmoc-Phe	Isobutyric Acid
74	Fmoc-Phe	Fmoc-Phe	Isovaleric Acid
75	Fmoc-Phe	Fmoc-Phe	4-Methylvaleric Acid
76	Fmoc-Phe	Fmoc-Phe	Trimethylacetic Acid
77	Fmoc-Phe	Fmoc-Phe	tert-Butylacetic Acid
78	Fmoc-Phe	Fmoc-Phe	Cyclohexane-carboxylic Acid
79	Fmoc-Phe	Fmoc-Phe	Cyclohexylacetic Acid
80	Fmoc-Phe	Fmoc-Phe	Cyclohexanebutyric Acid
81	Fmoc-Phe	Fmoc-Phe	Cycloheptanecarboxylic Acid
82	Fmoc-Phe	Fmoc-Phe	Acetic Acid
83	Fmoc-Phe	Fmoc-Phe	Cyclobutanecarboxylic Acid
84	Fmoc-Phe	Fmoc-Phe	Cyclopentanecarboxylic Acid
85	Fmoc-Phe	Fmoc-Phe	Cyclohexanepropionic Acid
86	Fmoc-Phe	Fmoc-Phe	4-Methyl-1-cyclohexane-carboxylic Acid
87	Fmoc-Phe	Fmoc-Phe	4-tert-Butyl-cyclohexane-carboxylic Acid
88	Fmoc-Phe	Fmoc-Phe	1-Adamantaneacetic Acid
89	Fmoc-Phe	Fmoc-Phe	3-3-diphenyl propionic Acid
90	Fmoc-Phe	Fmoc-Phe	Dicyclohexylacetic Acid
91	Fmoc-Phe	Fmoc-Phe	Indole-3-acetic acid
92	Fmoc-Phe	Fmoc-Phe	1-Naphthyl acetic acid
93	Fmoc-Phe	Fmoc-Phe	3-(3,4,5)-Trimethoxyphenyl propionic Acid
94	Fmoc-Phe	Fmoc-Phe	2-Norbornaneacetic Acid
95	Fmoc-Phe	Fmoc-Phe	Cyclopentylacetic Acid
96	Fmoc-Phe	Fmoc-Phe	2-Ethyl butyric acid

Example 3: Preparation of Libraries of N-Methyl- and N-Benzyl-1,4,5-trisubstituted-2,3-diketopiperazines

Libraries of N-methyl- and N-benzyl-1,4,5-trisubstituted-2,3-diketopiperazines were prepared. Here, whereas a single reagent was used to provide each of the R groups of the interemediates prepared in the syntheses of the individual compounds of Examples 1 and 2, both single reactants and mixtures of reactants were used to provide the R^1, R^3 and R^4 groups for the different library pools that were synthesiszed. As is discussed in greated detail below, 29 library pools were prepared in which R^1 was an individual amino acid side chain, and with R^3 and R^4 being separate mixtures of amino acid side chains (R^3) and carboxylic acid chains (R^4).

Where individual reactants were used to provide a particular R group, the procedures of Examples 1 and 2 were followed. Where mixtures were desired at a particular R group, the protected amino acids or carboxylic acids were provided in mixtures. The mixtures used to provide the various R groups are listed in Table 4, below, with the relative molar amount of each reactant being listed.

Table 4

Mixtures of Reactants Used to Prepare Resin-bound N-Methyl- and N-Benzyl-1,4,5-trisubstituted-2,3-diketopiperazine Library
Intermediates 1,3 and 4 of Scheme 1

Fmoc-R^1aaOH		Fmoc-R^3aaOH		R^4COOH	
Relative Mole	Ratio	Relative Mole	Ratio	Relative Mole	Ratio
Fmoc-Ala	0.833	Fmoc-Ala	0.833	1-Phenyl-1-cyclo-propane-carboxylic Acid	1.00
Fmoc-Phe	0.61	Fmoc-Phe	0.61	m-Tolylacetic Acid	1.80
Fmoc-Gly	1	Fmoc-Gly	1	3-Fluorophenyl-acetic Acid	0.84
Fmoc-Ile	1.201	Fmoc-Ile	1.201	(α,α,α-Trifluoro-m-tolyl)acetic Acid	0.61
Fmoc-Lys(Boc)	1.016	Fmoc-Leu	0.932	3-Methoxy-phenylacetic Acid	1.17
Fmoc-Leu	0.932	Fmoc-Met(O)	0.567	4-Methoxy-phenylacetic Acid	1.80
Fmoc-Met(O)	0.567	Fmoc-Ser(tBut)	0.639	4-Ethoxyphenyl-acetic Acid	1.40
Fmoc-Ser(tBut)	0.639	Fmoc-Thr(tBut)	0.865	4-Isobutyl-α-methylphenyl-acetic Acid	1.70
Fmoc-Thr(tBut)	0.865	Fmoc-Val	1.136	3,4-Dichloro-phenylacetic Acid	0.81
Fmoc-Val	1.136	Fmoc-Tyr(tBut)	0.672	3,5-Bis(trifluoro-methyl)phenyl-acetic Acid	0.50
Fmoc-Tyr(tBut)	0.672	Fmoc-ala	0.833	Phenylacetic Acid	1.00
Fmoc-ala	0.833	Fmoc-phe	0.61	Hydrocinnamic Acid	2.50

Fmoc-phe	0.61	Fmoc-ile	1.201	4-Phenylbutyric Acid	3.00
Fmoc-ile	1.201	Fmoc-leu	0.932	Butyric Acid	3.39
Fmoc-lys(Boc)	1.016	Fmoc-ser(tBut)	0.639	Heptanoic Acid	3.51
Fmoc-leu	0.932	Fmoc-thr(tBut)	0.865	Isobutyric Acid	3.11
Fmoc-ser(tBut)	0.639	Fmoc-val	1.136	Isovaleric Acid	6.36
Fmoc-thr(tBut)	0.865	Fmoc-tyr(tBut)	0.672	4-Methylvaleric Acid	3.32
Fmoc-val	1.136	Fmoc-Nle	0.938	Trimethylacetic Acid	4.24
Fmoc-tyr(tBut)	0.672	Fmoc-nle	0.938	tert-Butylacetic Acid	1.00
Fmoc-Nle	0.938	Fmoc-Nva	0.963	Cyclohexane-carboxylic Acid	3.51
Fmoc-nle	0.938	Fmoc-nva	0.963	Cyclohexyl-acetic Acid	3.95
Fmoc-Nva	0.963	Fmoc-NapAla	0.672	Cyclohexane-butyric Acid	3.33
Fmoc-nva	0.963	Fmoc-napala	0.672	Cycloheptane-carboxylic Acid	2.60
Fmoc-NapAla	0.672	Fmoc-Phg	0.483	Acetic Acid	2.65
Fmoc-napala	0.672	Fmoc-ChAla	0.943	Cyclobutane-carboxylic Acid	2.77
Fmoc-Phg	0.483	Fmoc-chala	0.943	Cyclopentane-carboxylic Acid	3.03
Fmoc-ChAla	0.943			3-Cyclopentyl-propionic Acid	3.71
Fmoc-chala	0.943			Cyclohexane-propionic Acid	2.80
				4-Methyl-1-cyclohexane-carboxylic Acid	5.92
				4-tert-Butyl-cyclohexane-carboxylic Acid	6.64
				1-Adamantane-acetic Acid	11.16

3,3-Diphenyl-propionic Acid	2.80
Dicyclohexyl-acetic Acid	1.00
Indole-3-acetic Acid	1.16
1-Napthyl-acetic Acid	3.00
3-(3,4,5)-Tri-methoxyphenyl-propionic Acid	2.00
2-Norbornane-acetic Acid	3.00
Cyclopentyl-acetic Acid	1.00
2-Ethylbutyric Acid	1.50

A. Typical procedure for the first Fmoc-amino acid mixture coupling.

p-Methylbenzydrylamine (MBHA; 100 mg) resin (1.0 meq/g, 100-200 mesh) was contained within a sealed polypropylene mesh packet. Following neutralization with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM; 3x5mL), the resin was washed with DCM (3x5mL). A 0.5M solution of mixed Fmoc amino acids in DMF (1.2 mL) at a predetermined molar ratio (6X, 0.6 meq total), 1.2 mL 0.5M 1-hydroxybenzo-triazole (HOBt, 6X, 0.6 meq) in DMF, and 1.2 mL 0.5M diisopropylcarbodiimide (DIPCDI, 6X, 0.6 meq) in DMF were prereacted for 15 minutes for a final concentration of each of 0.167M. The resin packet was then added to the solution and permitted to react

for 120 minutes. Following the reaction, the solution was decanted and the resin washed with DMF (3x5mL).

B. Typical procedure for the second Fmoc-amino acid mixture coupling.

Following deprotection as discussed before, the resin packet was neutralized with 5% diisopropyl-ethylamine (DIEA) in dichloromethane (DCM) (3x5mL) and then washed with DCM (3x5mL). A 0.5M solution of mixed Fmoc amino acids in DMF (1.2 mL) at a predetermined molar ratio (6X, 0.6 meq total), 1.2 mL 0.5M 1-hydroxy-benzotriazole (HOBt, 6X, 0.6 meq) in DMF, and 1.2 mL 0.5M diisopropylcarbodiimide (DIPCDI, 6X, 0.6 meq) in DMF were prereacted for 15 minutes for a final concentration of each of 0.167M. The resin packet was then added to the solution and permitted to react for 120 minutes. Following the reaction, the solution was decanted and the resin washed with DMF (3x5mL).

C. Typical procedure for a carboxylic acid mixture coupling.

Following deprotection, the resin packet was neutralized with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM) (3x5mL) and then washed with DCM (3x5mL). A 0.5M solution of carboxylic acids in DMF (2.0 mL) at a predetermined molar ratio (10X, 1.0 meq total), 2.0 mL 0.5M 1-hydroxybenzotriazole (HOBt, 10X, 1.0 meq) in DMF, and 2.0 mL 0.5M diisopropyl-carbodiimide (DIPCDI, 10X, 1.0 meq) in DMF was prereacted for 15 minutes for a final concentration

of each of 0.167M. The resin packet was then added to the solution and permitted to react for 120 minutes. Following the reaction, the solution was decanted and the resin washed with DMF (3x5mL).

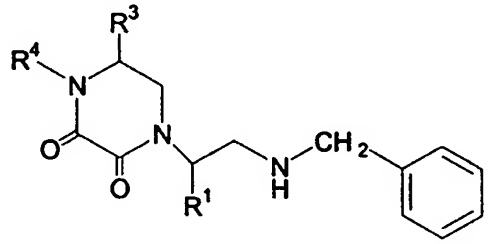
N-Alkylations on the resin-bound peptides and peptide mixtures were carried out as described in Examples 1 and 2 for the individual compounds. Reductions of the resin-bound N-acylated and N-alkylated peptide mixtures were carried out as discussed in Examples 1 and 2 for the individual compounds. Cyclization reactions and cleavage of the compound libraries on and from the resin were also carried out as described in Examples 1 and 2 for the individual peptides.

These libraries were positional scanning libraries in that each position of R^1, R^3 and R^4 was separately occupied by a single substituent group (O), whereas each of the remaining two positions was occupied by approximately equimolar mixtures of all of the substituent groups used at each position (X and X). In these libraries, 27 amino acids were used at the R^1 position, 29 amino acids were used at the R^3 position and 40 carboxylic acids were used at the R^4 position. Thus, for each of the R^1 positions scanned (OXX), there were a mixture of 1080 compounds present (1x27x40). There were 1160 compounds present (29x1x40) for each of the scanned R^3 positions (XOX), with 783 compounds being present (29x27x1) in each mixture when the R^4 position (XXO) was scanned. The three mixtures provided a total diversity of 31,320

compounds (29x27x40). The various amino acids and carboxylic acids used to prepare these libraries are listed in Tables 5 and 6 hereinafter.

Table 5

N-Benzyl-1,4,5-trisubstituted-
2,3-diketopiperazine Library



Pool No.	R^1	R^3	R^4
1	Fmoc-Ala	X	X
2	Fmoc-Phe	X	X
3	Fmoc-Gly	X	X
4	Fmoc-Ile	X	X
5	Fmoc-Lys(Boc)	X	X
6	Fmoc-Leu	X	X
7	Fmoc-Met(O)	X	X
8	Fmoc-Ser(tBut)	X	X
9	Fmoc-Thr(tBut)	X	X
10	Fmoc-Val	X	X
11	Fmoc-Tyr(tBut)	X	X
12	Fmoc-ala	X	X
13	Fmoc-phe	X	X
14	Fmoc-ile	X	X
15	Fmoc-lys(Boc)	X	X
16	Fmoc-leu	X	X
17	Fmoc-ser(tBut)	X	X

18	Fmoc-thr(tBut)	X	X
19	Fmoc-val	X	X
20	Fmoc-tyr(tBut)	X	X
21	Fmoc-Nle	X	X
22	Fmoc-nle	X	X
23	Fmoc-Nva	X	X
24	Fmoc-nva	X	X
25	Fmoc-NapAla	X	X
26	Fmoc-napala	X	X
27	Fmoc-Phg	X	X
28	Fmoc-ChAla	X	X
29	Fmoc-chala	X	X

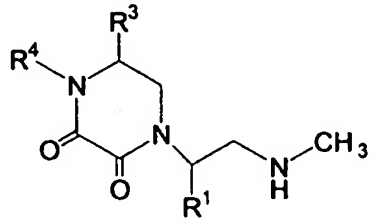
30	X	Fmoc-Ala	X
31	X	Fmoc -Phe	X
32	X	Fmoc-Gly	X
33	X	Fmoc-Ile	X
34	X	Fmoc-Leu	X
35	X	Fmoc-Met(O)	X
36	X	Fmoc-Ser(tBut)	X
37	X	Fmoc-Thr(tBut)	X
38	X	Fmoc-Val	X
39	X	Fmoc-Tyr(tBut)	X
40	X	Fmoc-ala	X
41	X	Fmoc-phe	X
42	X	Fmoc-ile	X
43	X	Fmoc-leu	X
44	X	Fmoc-ser(tBut)	X
45	X	Fmoc-thr(tBut)	X
46	X	Fmoc-val	X
47	X	Fmoc-tyr(tBut)	X
48	X	Fmoc-Nle	X
49	X	Fmoc-nle	X
50	X	Fmoc-Nva	X
51	X	Fmoc-nva	X
52	X	Fmoc-NapAla	X
53	X	Fmoc-napala	X
54	X	Fmoc-Phg	X
55	X	Fmoc-ChAla	X
56	X	Fmoc-chala	X

57	X	X	1-Phenyl-1-cyclo-propanecarboxylic Acid
58	X	X	m-Tolylacetic Acid
59	X	X	3-Fluorophenyl acetic Acid
60	X	X	(α,α,α–Trifluoro-m-tolyl)acetic Acid
61	X	X	p-Tolylacetic Acid
62	X	X	3-Methoxyphenyl-acetic Acid
63	X	X	4-Methoxyphenyl-acetic Acid
64	X	X	4-Ethoxyphenyl-acetic Acid
65	X	X	4-Isobutyl-α-methyl-phenylacetic Acid
66	X	X	3,4-Dichloro-phenylacetic Acid
67	X	X	3,5-Bis-(trifluoromethyl)-phenylacetic Acid
68	X	X	Phenylacetic Acid
69	X	X	Hydrocinnamic Acid
70	X	X	4-Phenylbutyric Acid
71	X	X	Butyric Acid
72	X	X	Heptanoic Acid
73	X	X	Isobutyric Acid
74	X	X	Isovaleric Acid
75	X	X	4-Methylvaleric Acid
76	X	X	Trimethylacetic Acid
77	X	X	tert-Butylacetic Acid
78	X	X	Cyclohexane-carboxylic Acid
79	X	X	Cyclohexyl-acetic Acid
80	X	X	Cyclohexane-butyric Acid
81	X	X	Cycloheptane-carboxylic Acid

82	X	X	Acetic Acid
83	X	X	Cyclobutane-carboxylic Acid
84	X	X	Cyclopentane-carboxylic Acid
85	X	X	Cyclohexane-propionic Acid
86	X	X	4-Methyl-1-cyclohexane-carboxylic Acid
87	X	X	4-tert-Butyl-cyclohexane-carboxylic Acid
88	X	X	1-Adamantane-acetic Acid
89	X	X	3-3-Diphenyl-propionic Acid
90	X	X	Dicyclohexyl-acetic Acid
91	X	X	Indole-3-acetic Acid
92	X	X	1-Naphthylacetic Acid
93	X	X	3-(3,4,5)-Tri-methoxyphenyl propionic Acid
94	X	X	2-Norbornane-acetic Acid
95	X	X	Cyclopentyl acetic Acid
96	X	X	2-Ethylbutyric Acid

Table 6

N-Methyl-1,4,5-trisubstituted-
2,3-diketopiperazine Library



Pool No.	R^1	R^3	R^4
1	Fmoc-Ala	X	X
2	Fmoc-Phe	X	X
3	Fmoc-Gly	X	X
4	Fmoc-Ile	X	X
5	Fmoc-Lys(Boc)	X	X
6	Fmoc-Leu	X	X
7	Fmoc-Met(O)	X	X
8	Fmoc-Ser(tBut)	X	X
9	Fmoc-Thr(tBut)	X	X
10	Fmoc-Val	X	X
11	Fmoc-Tyr(tBut)	X	X
12	Fmoc-ala	X	X
13	Fmoc-phe	X	X
14	Fmoc-ile	X	X
15	Fmoc-lys(Boc)	X	X
16	Fmoc-leu	X	X
17	Fmoc-ser(tBut)	X	X
18	Fmoc-thr(tBut)	X	X
19	Fmoc-val	X	X
20	Fmoc-tyr(tBut)	X	X
21	Fmoc-Nle	X	X
22	Fmoc-nle	X	X
23	Fmoc-Nva	X	X
24	Fmoc-nva	X	X
25	Fmoc-NapAla	X	X

26	Fmoc-napala	X	X	
27	Fmoc-Phg	X	X	
28	Fmoc-ChAla	X	X	
29	Fmoc-chala	X	X	
30	X	Fmoc-Ala	X	
31	X	Fmoc -Phe	X	
32	X	Fmoc-Gly	X	
33	X	Fmoc-Ile	X	
34	X	Fmoc-Leu	X	
35	X	Fmoc-Met(O)	X	
36	X	Fmoc-Ser(tBut)	X	
37	X	Fmoc-Thr(tBut)	X	
38	X	Fmoc-Val	X	
39	X	Fmoc-Tyr(tBut)	X	
40	X	Fmoc-ala	X	
41	X	Fmoc-phe	X	
42	X	Fmoc-ile	X	
43	X	Fmoc-leu	X	
44	X	Fmoc-ser(tBut)	X	
45	X	Fmoc-thr(tBut)	X	
46	X	Fmoc-val	X	
47	X	Fmoc-tyr(tBut)	X	
48	X	Fmoc-Nle	X	
49	X	Fmoc-nle	X	
50	X	Fmoc-Nva	X	
51	X	Fmoc-nva	X	
52	X	Fmoc-NapAla	X	
53	X	Fmoc-napala	X	
54	X	Fmoc-Phg	X	
55	X	Fmoc-ChAla	X	
56	X	Fmoc-chala	X	
57	X	X	1-Phenyl-1-cyclo-propanecarboxylic Acid	
58	X	X	m-Tolylacetic Acid	
59	X	X	3-Fluorophenyl-acetic Acid	

60	X	X	(α,α,α–Trifluoro-m-tolyl)acetic Acid
61	X	X	p-Tolylacetic Acid
62	X	X	3-Methoxyphenyl-acetic Acid
63	X	X	4-Methoxyphenyl-acetic Acid
64	X	X	4-Ethoxyphenyl-acetic Acid
65	X	X	4-Isobutyl-α–methyl-phenylacetic Acid
66	X	X	3,4-Dichloro-phenylacetic Acid
67	X	X	3,5-Bis-(trifluoromethyl)-phenylacetic Acid
68	X	X	Phenylacetic Acid
69	X	X	Hydrocinnamic Acid
70	X	X	4-Phenylbutyric Acid
71	X	X	Butyric Acid
72	X	X	Heptanoic Acid
73	X	X	Isobutyric Acid
74	X	X	Isovaleric Acid
75	X	X	4-Methylvaleric Acid
76	X	X	Trimethylacetic Acid
77	X	X	tert-Butylacetic Acid
78	X	X	Cyclohexane-carboxylic Acid
79	X	X	Cyclohexyl-acetic Acid
80	X	X	Cyclohexane-butyric Acid
81	X	X	Cycloheptane-carboxylic Acid
82	X	X	Acetic Acid
83	X	X	Cyclobutane-carboxylic Acid
84	X	X	Cyclopentane-carboxylic Acid
85	X	X	Cyclohexane-propionic Acid

86	X	X	4-Methyl-1-cyclohexane-carboxylic Acid
87	X	X	4-tert-Butyl-cyclohexane-carboxylic Acid
88	X	X	1-Adamantane-acetic Acid
89	X	X	3-3-Diphenyl-propionic Acid
90	X	X	Dicyclohexyl-acetic Acid
91	X	X	Indole-3-acetic Acid
92	X	X	1-Naphthylacetic Acid
93	X	X	3-(3,4,5)-Tri-methoxyphenyl propionic Acid
94	X	X	2-Norbornane-acetic Acid
95	X	X	Cyclopentyl acetic Acid
96	X	X	2-Ethylbutyric Acid

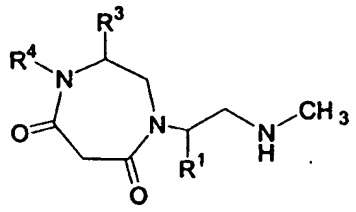
Example 4: Preparation of Individual N-Methyl-trisubstituted-5,7-diketo-1,4-diazacycloheptane Compounds and Library

A series of individual N-methyl-trisubstituted-5,7-diketo-1,4-diazacycloheptane compounds was prepared as discussed in Examples 1 and 2. The amino acids and carboxylic acids used to prepare these individual compounds are enumerated in Table 7, below.

Table 7

Individual N-Methyl-trisubstituted-5,7-diketo-1,4-diazacycloheptane

Compounds Synthesized



Prep	R^1	R^3	R^4
01	Fmoc-Ala	Fmoc-Phe	Phenylacetic Acid
02	Fmoc-Phe	Fmoc-Phe	Phenylacetic Acid
03	Fmoc-Gly	Fmoc-Phe	Phenylacetic Acid
04	Fmoc-Ile	Fmoc-Phe	Phenylacetic Acid
05	Fmoc-Lys(Boc)	Fmoc-Phe	Phenylacetic Acid
06	Fmoc-Leu	Fmoc-Phe	Phenylacetic Acid
07	Fmoc-Met(O)	Fmoc-Phe	Phenylacetic Acid
08	Fmoc-Ser(tBut)	Fmoc-Phe	Phenylacetic Acid
09	Fmoc-Thr(tBut)	Fmoc-Phe	Phenylacetic Acid
10	Fmoc-Val	Fmoc-Phe	Phenylacetic Acid
11	Fmoc-Tyr(tBut)	Fmoc-Phe	Phenylacetic Acid
12	Fmoc-ala	Fmoc-Phe	Phenylacetic Acid
13	Fmoc-phe	Fmoc-Phe	Phenylacetic Acid
14	Fmoc-ile	Fmoc-Phe	Phenylacetic Acid
15	Fmoc-lys(Boc)	Fmoc-Phe	Phenylacetic Acid
16	Fmoc-leu	Fmoc-Phe	Phenylacetic Acid
17	Fmoc-ser(tBut)	Fmoc-Phe	Phenylacetic Acid
18	Fmoc-thr(tBut)	Fmoc-Phe	Phenylacetic Acid
19	Fmoc-val	Fmoc-Phe	Phenylacetic Acid
20	Fmoc-tyr(tBut)	Fmoc-Phe	Phenylacetic Acid
21	Fmoc-Nle	Fmoc-Phe	Phenylacetic Acid
22	Fmoc-nle	Fmoc-Phe	Phenylacetic Acid
23	Fmoc-Nva	Fmoc-Phe	Phenylacetic Acid

24	Fmoc-nva	Fmoc-Phe	Phenylacetic Acid
25	Fmoc-NapAla	Fmoc-Phe	Phenylacetic Acid
26	Fmoc-napala	Fmoc-Phe	Phenylacetic Acid
27	Fmoc-Phg	Fmoc-Phe	Phenylacetic Acid
28	Fmoc-ChAla	Fmoc-Phe	Phenylacetic Acid
29	Fmoc-chala	Fmoc-Phe	Phenylacetic Acid
30	Fmoc-Phe	Fmoc-Ala	Phenylacetic Acid
31	Fmoc-Phe	Fmoc -Phe	Phenylacetic Acid
32	Fmoc-Phe	Fmoc-Gly	Phenylacetic Acid
33	Fmoc-Phe	Fmoc-Ile	Phenylacetic Acid
34	Fmoc-Phe	Fmoc-Leu	Phenylacetic Acid
35	Fmoc-Phe	Fmoc-Met(O)	Phenylacetic Acid
36	Fmoc-Phe	Fmoc-Ser(tBut)	Phenylacetic Acid
37	Fmoc-Phe	Fmoc-Thr(tBut)	Phenylacetic Acid
38	Fmoc-Phe	Fmoc-Val	Phenylacetic Acid
39	Fmoc-Phe	Fmoc-Tyr(tBut)	Phenylacetic Acid
40	Fmoc-Phe	Fmoc-ala	Phenylacetic Acid
41	Fmoc-Phe	Fmoc-phe	Phenylacetic Acid
42	Fmoc-Phe	Fmoc-ile	Phenylacetic Acid
43	Fmoc-Phe	Fmoc-leu	Phenylacetic Acid
44	Fmoc-Phe	Fmoc-ser(tBut)	Phenylacetic Acid
45	Fmoc-Phe	Fmoc-thr(tBut)	Phenylacetic Acid
46	Fmoc-Phe	Fmoc-val	Phenylacetic Acid
47	Fmoc-Phe	Fmoc-tyr(tBut)	Phenylacetic Acid
48	Fmoc-Phe	Fmoc-Nle	Phenylacetic Acid
49	Fmoc-Phe	Fmoc-nle	Phenylacetic Acid
50	Fmoc-Phe	Fmoc-Nva	Phenylacetic Acid
51	Fmoc-Phe	Fmoc-nva	Phenylacetic Acid
52	Fmoc-Phe	Fmoc-NapAla	Phenylacetic Acid
53	Fmoc-Phe	Fmoc-napala	Phenylacetic Acid
54	Fmoc-Phe	Fmoc-Phg	Phenylacetic Acid
55	Fmoc-Phe	Fmoc-ChAla	Phenylacetic Acid
56	Fmoc-Phe	Fmoc-chala	Phenylacetic Acid
57	Fmoc-Phe	Fmoc-Phe	1-Phenyl-1-cyclopropane-carboxylic Acid
58	Fmoc-Phe	Fmoc-Phe	m-Tolylacetic Acid
59	Fmoc-Phe	Fmoc-Phe	3-Fluorophenylacetic Acid
60	Fmoc-Phe	Fmoc-Phe	(α,α,α-Trifluoro-m-tolyl)-acetic Acid
61	Fmoc-Phe	Fmoc-Phe	p-Tolylacetic Acid

62	Fmoc-Phe	Fmoc-Phe	3-Methoxyphenylacetic Acid
63	Fmoc-Phe	Fmoc-Phe	4-Methoxyphenylacetic Acid
64	Fmoc-Phe	Fmoc-Phe	4-Ethoxyphenylacetic Acid
65	Fmoc-Phe	Fmoc-Phe	4-Isobutyl-α-methyl-phenylacetic Acid
66	Fmoc-Phe	Fmoc-Phe	3,4-Dichlorophenylacetic Acid
67	Fmoc-Phe	Fmoc-Phe	3,5-Bis(trifluoromethyl)-phenylacetic Acid
68	Fmoc-Phe	Fmoc-Phe	Phenylacetic Acid
69	Fmoc-Phe	Fmoc-Phe	Hydrocinnamic Acid
70	Fmoc-Phe	Fmoc-Phe	4-Phenylbutyric Acid
71	Fmoc-Phe	Fmoc-Phe	Butyric Acid
72	Fmoc-Phe	Fmoc-Phe	Heptanoic Acid
73	Fmoc-Phe	Fmoc-Phe	Isobutyric Acid
74	Fmoc-Phe	Fmoc-Phe	Isovaleric Acid
75	Fmoc-Phe	Fmoc-Phe	4-Methylvaleric Acid
76	Fmoc-Phe	Fmoc-Phe	Trimethylacetic Acid
77	Fmoc-Phe	Fmoc-Phe	tert-Butylacetic Acid
78	Fmoc-Phe	Fmoc-Phe	Cyclohexanecarboxylic Acid
79	Fmoc-Phe	Fmoc-Phe	Cyclohexylacetic Acid
80	Fmoc-Phe	Fmoc-Phe	Cyclohexanebutyric Acid
81	Fmoc-Phe	Fmoc-Phe	Cycloheptanecarboxylic Acid
82	Fmoc-Phe	Fmoc-Phe	Acetic Acid
83	Fmoc-Phe	Fmoc-Phe	Cyclobutanecarboxylic Acid
84	Fmoc-Phe	Fmoc-Phe	Cyclopentanecarboxylic Acid
85	Fmoc-Phe	Fmoc-Phe	Cyclohexanepropionic Acid
86	Fmoc-Phe	Fmoc-Phe	4-Methyl-1-cyclohexane-carboxylic Acid
87	Fmoc-Phe	Fmoc-Phe	4-tert-Butyl-cyclohexane-carboxylic Acid
88	Fmoc-Phe	Fmoc-Phe	1-Adamantaneacetic Acid

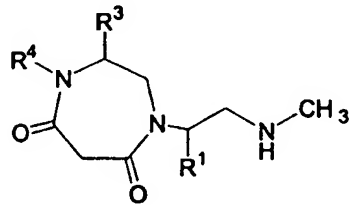
89	Fmoc-Phe	Fmoc-Phe	3-3-diphenyl propionic Acid
90	Fmoc-Phe	Fmoc-Phe	Dicyclohexylacetic Acid
91	Fmoc-Phe	Fmoc-Phe	Indole-3-acetic Acid
92	Fmoc-Phe	Fmoc-Phe	1-Naphthyl acetic Acid
93	Fmoc-Phe	Fmoc-Phe	3-(3,4,5)-Trimethoxyphenyl propionic Acid
94	Fmoc-Phe	Fmoc-Phe	2-Norbornaneacetic Acid
95	Fmoc-Phe	Fmoc-Phe	Cyclopentylacetic Acid
96	Fmoc-Phe	Fmoc-Phe	2-Ethyl butyric Acid

A library of N-methyl-trisubstituted-5,7-diketo-1,4-diazacycloheptane compounds was also prepared in a manner similar to that discussed for Example 3, except that malonyl dichloride as the ring-forming reagent. The amino acids and carboxylic acids used to prepare the compound pools of this library are shown in Table 8, below.

Table 8

N-Methyl-trisubstituted-5,7-diketo-1,4-diazacycloheptane

Compound Library



Pool No.	R^1	R^3	R^4
1	Fmoc-Ala	X	X
2	Fmoc -Phe	X	X
3	Fmoc-Gly	X	X
4	Fmoc-Ile	X	X
5	Fmoc-Lys(Boc)	X	X
6	Fmoc-Leu	X	X
7	Fmoc-Met(O)	X	X
8	Fmoc-Ser(tBut)	X	X
9	Fmoc-Thr(tBut)	X	X
10	Fmoc-Val	X	X
11	Fmoc-Tyr(tBut)	X	X
12	Fmoc-ala	X	X
13	Fmoc-phe	X	X
14	Fmoc-ile	X	X
15	Fmoc-lys(Boc)	X	X
16	Fmoc-leu	X	X
17	Fmoc-ser(tBut)	X	X
18	Fmoc-thr(tBut)	X	X
19	Fmoc-val	X	X
20	Fmoc-tyr(tBut)	X	X
21	Fmoc-Nle	X	X
22	Fmoc-nle	X	X
23	Fmoc-Nva	X	X
24	Fmoc-nva	X	X
25	Fmoc-NapAla	X	X
26	Fmoc-napala	X	X
27	Fmoc-Phg	X	X
28	Fmoc-ChAla	X	X
29	Fmoc-chala	X	X
30	X	Fmoc-Ala	X
31	X	Fmoc -Phe	X
32	X	Fmoc-Gly	X
33	X	Fmoc-Ile	X
34	X	Fmoc-Leu	X
35	X	Fmoc-Met(O)	X
36	X	Fmoc-Ser(tBut)	X
37	X	Fmoc-Thr(tBut)	X

38	X	Fmoc-Val	X
39	X	Fmoc-Tyr(tBut)	X
40	X	Fmoc-ala	X
41	X	Fmoc-phe	X
42	X	Fmoc-ile	X
43	X	Fmoc-leu	X
44	X	Fmoc-ser(tBut)	X
45	X	Fmoc-thr(tBut)	X
46	X	Fmoc-val	X
47	X	Fmoc-tyr(tBut)	X
48	X	Fmoc-Nle	X
49	X	Fmoc-nle	X
50	X	Fmoc-Nva	X
51	X	Fmoc-nva	X
52	X	Fmoc-NapAla	X
53	X	Fmoc-napala	X
54	X	Fmoc-Phg	X
55	X	Fmoc-ChAla	X
56	X	Fmoc-chala	X

57	X	X	1-Phenyl-1-cyclo-propanecarboxylic Acid
58	X	X	m-Tolylacetic Acid
59	X	X	3-Fluorophenyl-acetic Acid
60	X	X	(α,α,α–Trifluoro-m-tolyl)acetic Acid
61	X	X	p-Tolylacetic Acid
62	X	X	3-Methoxyphenyl-acetic Acid
63	X	X	4-Methoxyphenyl-acetic Acid
64	X	X	4-Ethoxyphenyl-acetic Acid
65	X	X	4-Isobutyl-α-methyl-phenylacetic Acid
66	X	X	3,4-Dichloro-phenylacetic Acid
67	X	X	3,5-Bis-(trifluoromethyl)-phenylacetic Acid

68	X	X	Phenylacetic Acid
69	X	X	Hydrocinnamic Acid
70	X	X	4-Phenylbutyric Acid
71	X	X	Butyric Acid
72	X	X	Heptanoic Acid
73	X	X	Isobutyric Acid
74	X	X	Isovaleric Acid
75	X	X	4-Methylvaleric Acid
76	X	X	Trimethylacetic Acid
77	X	X	tert-Butylacetic Acid
78	X	X	Cyclohexane-carboxylic Acid
79	X	X	Cyclohexyl-acetic Acid
80	X	X	Cyclohexane-butyric Acid
81	X	X	Cycloheptane-carboxylic Acid
82	X	X	Acetic Acid
83	X	X	Cyclobutane-carboxylic Acid
84	X	X	Cyclopentane-carboxylic Acid
85	X	X	Cyclohexane-propionic Acid
86	X	X	4-Methyl-1-cyclohexane-carboxylic Acid
87	X	X	4-tert-Butyl-cyclohexane-carboxylic Acid
88	X	X	1-Adamantane-acetic Acid
89	X	X	3-3-Diphenyl-propionic Acid
90	X	X	Dicyclohexyl-acetic Acid
91	X	X	Indole-3-acetic Acid
92	X	X	1-Naphthylacetic Acid

93	X	X	3-(3,4,5)-Trimethoxy-phenylpropionic Acid
94	X	X	2-Norbornane-acetic Acid
95	X	X	Cyclopentyl acetic Acid
96	X	X	2-Ethyibutyric Acid

Example 5: Preparation of Compounds with Additional Cyclizing Reagents

A series of ninety-nine individual compounds was prepared using eleven reagents for forming N-methylamino-substituted cyclic bis-amide and bis-amine compounds. The cyclization reactions from common N-methylated indermediate compound 5 of Scheme 1 are illustrated in Schemes 6 and 7, below. The amino acids and carboxylic acids used to form the R^1, R^3 and R^4 substituents are shown in Table 9 below.

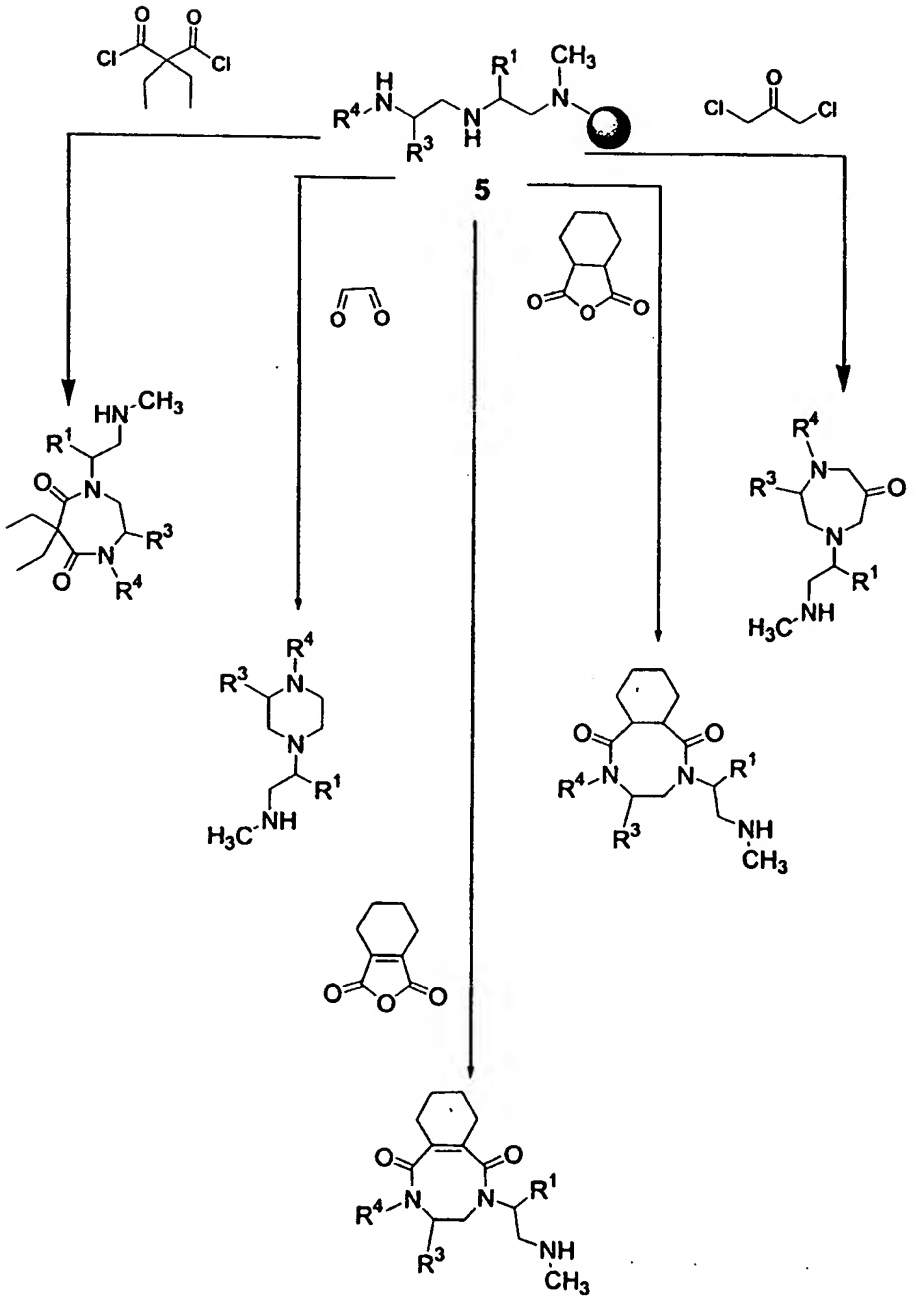
Table 9

Components of Intermediates 5 for Synthesis of Ninty-nine Individual Compounds

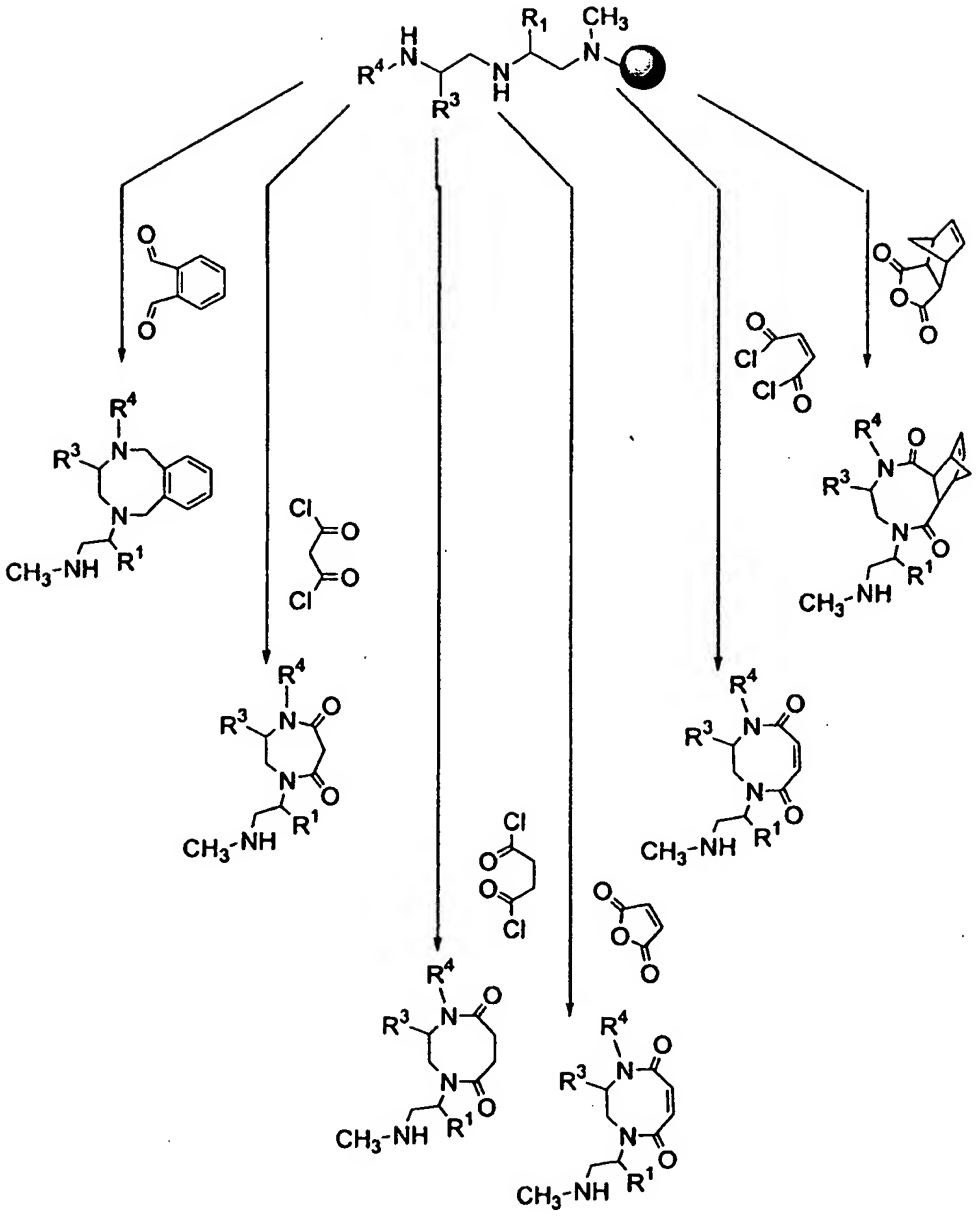
R^1	R^3	R^4
Phe	Phe	Phenylacetic Acid
Val	Phe	Phenylacetic Acid
Leu	Phe	Phenylacetic Acid
Phe	Gly	Phenylacetic Acid
Val	Gly	Phenylacetic Acid
Leu	Gly	Phenylacetic Acid

Phe	Leu	Phenylacetic Acid
Val	Leu	Phenylacetic Acid
Leu	Leu	Phenylacetic Acid

Scheme 6



Scheme 7



Example 6: Orphanin Binding Screen using the N-Benzyl-1,4,5-trisubstituted-2,3-diketopiperazine Library

A (para-iodo-Phe^1,para-iodo-Phe^4-) Orphanin FQ analogue was synthesized on the COMPASS multiple peptide synthesizer (Spyder, San Diego, CA). Tritiation of the iodo-compound was performed at the National Tritium Labeling Facility (Berkeley, CA). The ditritio-compound was obtained through hydrogen exchange in the presence of a catalyst. The diiodo-peptide (5 mg), dissolved in 1 mL of N,N-dimethylformamide (DMF), was exposed to tritium gas in the presence of 3 mg of palladium oxide. The reaction was allowed to proceed for two hours, after which the gas flow was discontinued and 2 mLs of methanol were added to the reaction mixture to exchange unreacted tritium. The resulting mixture was passed through Teflon filters (PTFE), which were rinsed with 50% aqueous DMF. The eluent was lyophilized to dryness overnight (about 18 hours). The tritiated peptide was purified by RP-HPLC. The radiolabeled peptide was found to have a specific activity of 33 Ci/mmole.

Frozen rat brains (Harlan, Indianapolis, IN) were defrosted in Tris buffer [50 mM Tris, 2 mM EDTA, 100 M phenylmethylsulphonylfluoride (PMSF), pH 7.4]. Individual brains, minus cerebella, were homogenized in 40 mLs of buffer in a glass Dounce homogenizer. Homogenates were spun for 10 minutes at 38,000 g (Beckmann H2-JC, Fullerton, CA). Pellets were resuspended in fresh buffer. The suspension was

incubated at 37°C for 30 minutes, and centrifuged for 10 minutes. Pellets were resuspended in 100 volumes of buffer. Samples were removed for protein concentration determinations using the method described by Bradford, *Anal. Biochem.*, 72:248 (1976) and bovine serum albumin as the standard. Bovine serum albumin (2 mg/mL) was added to the final suspension.

For association studies, each assay tube contained a final concentration of 1.8 nM [$^3H_2$]-Orphanin FQ, 1 mL of membrane suspension in a total volume of 1.1 mLs. The non-radiolabeled peptide (5 µM) was used to determine nonspecific binding. Assays were incubated at 25 C for time periods ranging from 5-30 minutes. The assay was performed twice. The reaction was terminated by filtration through GF-B filters using a Brandell Harvester (Gaithersberg, MA.) The filters had been previously soaked in 0.1% polyethyleneimine for one hour to reduce nonspecific binding. Filters were washed with 12 mL/sample Tris buffer at 4°C. Bound radioactivity was counted on a Beckmann Liquid Scintillation Counter (Fullerton, CA) and expressed in counts per minute. Saturation curves were obtained by incubating (2 hours) [$^3H_2$]-Orphanin FQ at 10 different concentrations from 0.7-27 nM in a final volume of 0.65 mL.

Nonspecific binding was determined in the presence of 5 µM Orphanin FQ. Saturation studies were carried out using four replicates, and the assay

was repeated three times. The reaction was terminated by filtration through GF-B filters, previously soaked in 0.1% polyethyleneimine, using a Tomtec 96 harvester (Orange, CT). Filters were washed with 6 mL/sample Tris buffer at 4°C. Bound radioactivity was counted on a Pharmacia Biotech Beta-plate Liquid Scintillation Counter (Piscataway, NJ) and expressed in counts per minute. Competition assays were performed as described for saturation studies. Standards for competition curves were obtained using cold competitor (Orphanin FQ) at seven different concentrations ranging from 0.009-9,000 nM. IC_{50} values were determined using six concentrations of each peptide analog.

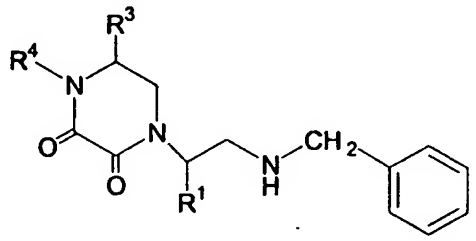
Competition studies were carried out in the presence of 3 nM [$^3H_2$]-Orphanin FQ. Competition studies were carried out using two replicates, and the assay was repeated four times. Dissociation constants (Kd), the maximum binding capacities (Bmax), and IC_{50} values were calculated using EBDA and LIGAND [Munson et al., *Anal. Biochem.*,107:220(1980)] or Graphpad/Prizm (ISI, San Diego, CA).

Results of these binding studies for the N-benzyl-1,4,5-trisubstituted-2,3-diketopiperazine library are provided in Table 10, below, with the data being shown in terms of the mean binding result (mean), the non-specific binding result that is subtracted from the mean (less NSB) and the value of 1/(percent bound) for each library pool of compounds. An "X" in the Table indicates that the particular R

group is comprised of a mixture of the several amino acid side chains or carboxylic acid chains used in preparation of the library.

Table 10

N-Benzyl-1,4,5-trisubstituted-
2,3-diketopiperazine Library
Orphanin Binding Inhibition Assay



Pool No.	R^1	R^3	R^4	Mean	Minus NSB	1 %Bound
1	Fmoc-Ala	X	X	2821.1	2212.10	0.010
2	Fmoc-Phe	X	X	2251	1642.00	0.014
3	Fmoc-Gly	X	X	2282.65	1673.65	0.014
4	Fmoc-Ile	X	X	2760.6	2151.60	0.011
5	Fmoc-Lys(Boc)	X	X	2079.55	1470.55	0.015
6	Fmoc-Leu	X	X	2450.9	1841.90	0.012
7	Fmoc-Met(O)	X	X	2738.05	2129.05	0.011
8	Fmoc-Ser(tBut)	X	X	2717.85	2108.85	0.011
9	Fmoc-Thr(tBut)	X	X	3005.05	2396.05	0.009
10	Fmoc-Val	X	X	2896.05	2287.05	0.010
11	Fmoc-Tyr(tBut)	X	X	2873.9	2264.90	0.010
12	Fmoc-ala	X	X	2641.25	2032.25	0.011
13	Fmoc-phe	X	X	1702.05	1093.05	0.021
14	Fmoc-ile	X	X	2817.15	2208.15	0.010
15	Fmoc-lys(Boc)	X	X	1527.9	918.90	0.025

16	Fmoc-leu	X	X	2460.35	1851.35	0.012
17	Fmoc-ser(tBut)	X	X	3003.65	2394.65	0.009
18	Fmoc-thr(tBut)	X	X	3047	2438.00	0.009
19	Fmoc-val	X	X	2363.25	1754.25	0.013
20	Fmoc-tyr(tBut)	X	X	2495.95	1886.95	0.012
21	Fmoc-Nle	X	X	2757.6	2148.60	0.011
22	Fmoc-nle	X	X	2615.25	2006.25	0.011
23	Fmoc-Nva	X	X	3077.7	2468.70	0.009
24	Fmoc-nva	X	X	2565.9	1956.90	0.012
25	Fmoc-NapAla	X	X	3269.8	2660.80	0.009
26	Fmoc-napala	X	X	2474.05	1865.05	0.012
27	Fmoc-Phg	X	X	2763.05	2154.05	0.011
28	Fmoc-ChAla	X	X	2722.1	2113.10	0.011
29	Fmoc-chala	X	X	2309.85	1700.85	0.013

30	X	Fmoc-Ala	X	1493.25	884.25	0.026
31	X	Fmoc -Phe	X	2522.15	1913.15	0.012
32	X	Fmoc-Gly	X	2556.75	1947.75	0.012
33	X	Fmoc-Ile	X	1806.1	1197.10	0.019
34	X	Fmoc-Leu	X	2223.3	1614.30	0.014
35	X	Fmoc-Met(O)	X	2216.8	1607.80	0.014
36	X	Fmoc-Ser(tBut)	X	1869.75	1260.75	0.018
37	X	Fmoc-Thr(tBut)	X	2391.1	1782.10	0.013
38	X	Fmoc-Val	X	1412.55	803.55	0.028
39	X	Fmoc-Tyr(tBut)	X	2255.4	1646.40	0.014
40	X	Fmoc-ala	X	2289	1680.00	0.013
41	X	Fmoc-phe	X	2743.5	2134.50	0.011
42	X	Fmoc-ile	X	2235.5	1626.50	0.014
43	X	Fmoc-leu	X	2652.75	2043.75	0.011
44	X	Fmoc-ser(tBut)	X	2738	2129.00	0.011
45	X	Fmoc-thr(tBut)	X	2866.4	2257.40	0.010
46	X	Fmoc-val	X	2646.55	2037.55	0.011
47	X	Fmoc-tyr(tBut)	X	2883.2	2274.20	0.010
48	X	Fmoc-Nle	X	2280.45	1671.45	0.014
49	X	Fmoc-nle	X	2402.65	1793.65	0.013
50	X	Fmoc-Nva	X	2142.8	1533.80	0.015
51	X	Fmoc-nva	X	2595.6	1986.60	0.011
52	X	Fmoc-NapAla	X	2770.2	2161.20	0.010
53	X	Fmoc-napala	X	2669.55	2060.55	0.011
54	X	Fmoc-Phg	X	2508.75	1899.75	0.012
55	X	Fmoc-ChAla	X	2448.75	1839.75	0.012
56	X	Fmoc-chala	X	2500.3	1891.30	0.012

57	X	X	1-Phenyl-1-cyclopropane carboxylic Acid	2705.3	2096.30	0.011
58	X	X	m-Tolylacetic Acid	2473.85	1864.85	0.012
59	X	X	3-Fluorophenyl-acetic Acid	2380.2	1771.20	0.013
60	X	X	(α,α,α-Trifluoro-m-tolyl)acetic Acid	2410.85	1801.85	0.013
61	X	X	p-Tolylacetic Acid	3147	2538.00	0.009
62	X	X	3-Methoxy-phenylacetic Acid	1550.15	941.15	0.024
63	X	X	4-Methoxy-phenylacetic Acid	1899.05	1290.05	0.018
64	X	X	4-Ethoxyphenyl-acetic Acid	1908.75	1299.75	0.017
65	X	X	4-Isobutyl-α-methylphenylacetic Acid	2712.35	2103.35	0.011
66	X	X	3,4-Dichloro-phenylacetic Acid	2205.25	1596.25	0.014
67	X	X	3,5-Bis(Trifluoro-methyl)phenyl acetic Acid	2814.9	2205.90	0.010
68	X	X	Phenylacetic Acid	2289.7	1680.70	0.013
69	X	X	Hydrocinnamic Acid	2539.3	1930.30	0.012
70	X	X	4-Phenylbutyric Acid	2653.25	2044.25	0.011
71	X	X	Butyric Acid	2479.05	1870.05	0.012
72	X	X	Heptanoic Acid	2214.45	1605.45	0.014
73	X	X	Isobutyric Acid	2232.9	1623.90	0.014
74	X	X	Isovaleric Acid	2526.6	1917.60	0.012
75	X	X	4-Methylvaleric Acid	2434.75	1825.75	0.012
76	X	X	Trimethylacetic Acid	2445.7	1836.70	0.012
77	X	X	tert-Butylacetic Acid	2671.55	2062.55	0.011
78	X	X	Cyclohexane-carboxylic Acid	2467.35	1858.35	0.012

79	X	X	Cyclohexyl-acetic Acid	2580.25	1971.25	0.011
80	X	X	Cyclohexane-butyric Acid	2583.55	1974.55	0.011
81	X	X	Cycloheptane-carboxylic Acid	2644.3	2035.30	0.011
82	X	X	Acetic Acid	2830.85	2221.85	0.010
83	X	X	Cyclobutane-carboxylic Acid	2625.5	2016.50	0.011
84	X	X	Cyclopentane-carboxylic Acid	2784.4	2175.40	0.010
85	X	X	Cyclohexane-propionic Acid	2836.75	2227.75	0.010
86	X	X	4-Methyl-1-cyclohexane-carboxylic Acid	2735.2	2126.20	0.011
87	X	X	4-tert-Butyl-cyclohexane-carboxylic Acid	3084.25	2475.25	0.009
88	X	X	1-Adamantane-acetic Acid	2539.75	1930.75	0.012
89	X	X	3,3-Diphenyl-propionic Acid	2445.7	1836.70	0.012
90	X	X	Dicyclohexyl-acetic Acid	2537.6	1928.60	0.012
91	X	X	Indole-3-acetic Acid	2796.4	2187.40	0.010
92	X	X	1-Naphthyl-acetic Acid	2269.9	1660.90	0.014
93	X	X	3-(3,4,5)-Tri-methoxyphenyl-propionic Acid	2390.7	1781.70	0.013
94	X	X	2-Norbomane-acetic Acid	2083.8	1474.80	0.015
95	X	X	Cyclopentyl - acetic Acid	2666	2057.00	0.011
96	X	X	2-Ethylbutyric Acid	2495.65	1886.65	0.012

The results of a binding study such as that above are often graphed using the 1/(percent bound) data provided above. However, merely scanning the data indicates that pools 13 and 15 provided the best

binding for R^1, pools 30 and 38 provided best binding for R^3 and pool 62 provided best binding for R^4.

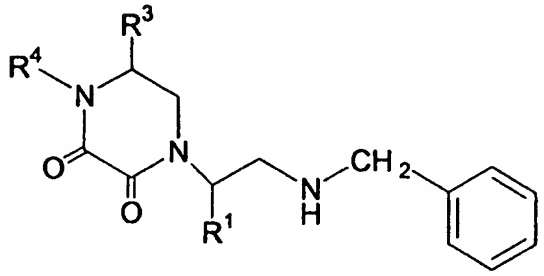
Example 7:Binding Inhibition of the Rat Brain Mu Receptor by Members of a N-Benzyl-1,4,5-trisubstituted-2,3-diketopiperazine Library

The previously prepared N-benzyl-1,4,5-trisubstituted-2,3-diketopiperazine library was screened for its ability to inhibit the binding of [^{3}H][D-Ala^2,MePhe^4,Gly^5-ol]enkephalin (DAMGO) that is known to bind specifically to the mu opiate receptor present in rat brain homogenates following literature procedures. [Dooley et al., *Science*, 266:2019(1994); U.S. Patent No. 5,763,193.]

Preparation of rat brain membranes and the receptor binding assay were carried out as described in Dooley et al., *Life Sci.*, 52:1509(1993). Each tube in the screening assay contained 0.08 mg of compound mixture per milliliter, 0.5 mL of membrane suspension (0.1 mg of protein), 7 nM ^{3}H-labeled DAMGO [specific activity 36 Ci/mmol, obtained from the National Institute on Drug Abuse (NIDA) repository through Chiron Mimotopes PeptideSystems (San Diego, CA) and 50mL ofpeptide mixture in 50 mM Tris-HCl buffer (pH 7.4). The final volume was 0.65 mL. The results of these screenings are shown below in Table 11, below. The results are reported in a manner similar to that discussed above, with the final results being reported as percent inhibition of DAMGO binding.

Table 11

N-Benzyl-1,4,5-trisubstituted-
2,3-diketopiperazine Library
Binding Inhibition of [^{3}H]DAMGO



Pool No.	R^1	R^3	R^4	Mean	Minus NSB	% Inhibition
1	Fmoc-Ala	X	X	795	568.0	26.1
2	Fmoc -Phe	X	X	305.6	78.6	89.8
3	Fmoc-Gly	X	X	701.0	474.0	38.4
4	Fmoc-Ile	X	X	693.4	466.4	39.4
5	Fmoc-Lys(Boc)	X	X	660.1	433.1	43.7
6	Fmoc-Leu	X	X	713.9	486.9	36.7
7	Fmoc-Met(O)	X	X	751.1	524.1	31.9
8	Fmoc-Ser(tBut)	X	X	953.0	726.0	5.6
9	Fmoc-Thr(tBut)	X	X	498.6	271.6	64.7
10	Fmoc-Val	X	X	753.9	526.9	31.5
11	Fmoc-Tyr(tBut)	X	X	681.8	454.8	40.9
12	Fmoc-ala	X	X	803.2	576.2	25.1
13	Fmoc-phe	X	X	469.9	242.9	68.4
14	Fmoc-ile	X	X	594.0	367.0	52.3
15	Fmoc-lys(Boc)	X	X	393.4	166.4	78.4
16	Fmoc-leu	X	X	585.3	358.3	53.4
17	Fmoc-ser(tBut)	X	X	964.4	737.4	4.1
18	Fmoc-thr(tBut)	X	X	859.7	632.7	17.7
19	Fmoc-val	X	X	375.3	148.3	80.7
20	Fmoc-tyr(tBut)	X	X	313.6	86.6	88.8
21	Fmoc-Nle	X	X	707	480.0	37.5

22	Fmoc-nle	X	X	601.4	374.4	51.3
23	Fmoc-Nva	X	X	733.1	506.1	34.2
24	Fmoc-nva	X	X	419.1	192.1	75.0
25	Fmoc-NapAla	X	X	459.8	232.8	69.7
26	Fmoc-napala	X	X	324.7	97.7	87.3
27	Fmoc-Phg	X	X	725.5	498.5	35.2
28	Fmoc-ChAla	X	X	445.3	218.3	71.6
29	Fmoc-chala	X	X	761.5	534.5	30.5
30	X	Fmoc-Ala	X	572.8	345.8	55.0
31	X	Fmoc -Phe	X	328.5	101.5	86.8
32	X	Fmoc-Gly	X	466.7	239.7	68.8
33	X	Fmoc-Ile	X	611.9	384.9	50.0
34	X	Fmoc-Leu	X	637.9	410.9	46.6
35	X	Fmoc-Met(O)	X	490	263.0	65.8
36	X	Fmoc-Ser(tBut)	X	847.9	620.9	19.3
37	X	Fmoc-Thr(tBut)	X	934.4	707.4	8.0
38	X	Fmoc-Val	X	751.1	524.1	31.9
39	X	Fmoc-Tyr(tBut)	X	541.9	314.9	59.1
40	X	Fmoc-ala	X	581.4	354.4	53.9
41	X	Fmoc-phe	X	522.6	295.6	61.6
42	X	Fmoc-ile	X	238.1	11.1	98.6
43	X	Fmoc-leu	X	512.5	285.5	62.9
44	X	Fmoc-ser(tBut)	X	611.2	384.2	50.1
45	X	Fmoc-thr(tBut)	X	697.8	470.8	38.8
46	X	Fmoc-val	X	251.2	24.2	96.9
47	X	Fmoc-tyr(tBut)	X	565.35	338.4	56.0
48	X	Fmoc-Nle	X	414.8	187.8	75.6
49	X	Fmoc-nle	X	506.4	279.4	63.7
50	X	Fmoc-Nva	X	506.4	279.4	63.7
51	X	Fmoc-nva	X	467.6	240.6	68.7
52	X	Fmoc-NapAla	X	853.7	626.7	18.5
53	X	Fmoc-napala	X	883.1	656.1	14.7
54	X	Fmoc-Phg	X	342.2	115.2	85.0
55	X	Fmoc-ChAla	X	878.6	651.6	15.3
56	X	Fmoc-chala	X	612.9	385.9	49.8
57	X	X	1-Phenyl-1-cyclo-propanecarboxylic Acid	351.7	124.7	83.8
58	X	X	m-Tolylacetic Acid	537.2	310.2	59.7
59	X	X	3-Fluorophenyl acetic Acid	506.4	279.4	63.7
60	X	X	(α,α,α--Trifluoro-m-tolyl)acetic Acid	545.3	318.3	58.6
61	X	X	p-Tolylacetic Acid	502.4	275.4	64.2

62	X	X	3-Methoxyphenyl-acetic Acid	447.4	220.4	71.4
63	X	X	4-Methoxyphenyl-acetic Acid	410.9	183.9	76.1
64	X	X	4-Ethoxyphenyl-acetic Acid	735.3	508.3	33.9
65	X	X	4-Isobutyl-α-methyl-phenylacetic Acid	850.6	623.6	18.9
66	X	X	3,4-Dichloro-phenylacetic Acid	536.6	309.6	59.7
67	X	X	3,5-Bis-(trifluoromethyl)-phenylacetic Acid	868.3	641.3	16.6
68	X	X	Phenylacetic Acid	557.1	330.1	57.1
69	X	X	Hydrocinnamic Acid	615.6	388.6	49.5
70	X	X	4-Phenylbutyric Acid	750.7	523.7	31.9
71	X	X	Butyric Acid	509.4	282.4	63.3
72	X	X	Heptanoic Acid	731.4	504.4	34.4
73	X	X	Isobutyric Acid	314.9	87.9	88.6
74	X	X	Isovaleric Acid	468.1	241.1	68.7
75	X	X	4-Methylvaleric Acid	579.3	352.3	54.2
76	X	X	Trimethylacetic Acid	335.4	108.4	85.9
77	X	X	tert-Butylacetic Acid	607.8	380.8	50.5
78	X	X	Cyclohexane-carboxylic Acid	468.2	241.2	68.6
79	X	X	Cyclohexyl-acetic Acid	712.5	485.5	36.9
80	X	X	Cyclohexane-butyric Acid	817.7	590.7	23.2
81	X	X	Cycloheptane-carboxylic Acid	606.1	379.1	50.7
82	X	X	Acetic Acid	667	440.0	42.8
83	X	X	Cyclobutane-carboxylic Acid	405.8	178.8	76.8
84	X	X	Cyclopentane-carboxylic Acid	421.9	194.9	74.7
85	X	X	Cyclohexane-propionic Acid	798.6	571.6	25.7

86	X	X	4-Methyl-1-cyclohexane-carboxylic Acid	770.2	543.2	29.4
87	X	X	4-tert-Butyl-cyclohexane -carboxylic Acid	809.7	582.7	24.2
88	X	X	1-Adamantane-acetic Acid	996.8	769.8	-0.10
89	X	X	3-3-Diphenyl-propionic Acid	745.3	518.3	32.6
90	X	X	Dicyclohexyl-acetic Acid	489.4	262.4	65.9
91	X	X	Indole-3-acetic Acid	730.0	503.0	34.6
92	X	X	1-Naphthylacetic Acid	472.2	245.2	68.1
93	X	X	3-(3,4,5)-Tri-methoxyphenyl propionic Acid	356	129.0	83.2
94	X	X	2-Norbomane-acetic Acid	673.2	446.2	42.0
95	X	X	Cyclopentyl acetic Acid	682.6	455.6	40.8
96	X	X	2-Ethylbutyric Acid	400.2	173.2	77.5

The results of a binding study such as that above are often graphed using the percent inhibition data provided above. However, merely scanning the data indicates that pools 2, 20 and 26 provided the best binding inhibition for R^1, pools 31, 42 and 46 provided best binding inhibition for R^3, and pools 57, 73, 76 and 93 provided best binding inhibition for R^4.

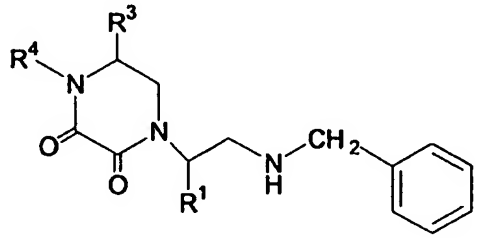
Example 8: Screening of a N-Benzyl-1,4,5-trisubstituted-2,3-diketopiperazine Library Binding in hORL-CHO Cells

The human ORL_1 receptor is the human equivalent of the murine Orphanin receptor that naturally binds to a pituitary peptide dynorphin A, as discussed in Example 6. Mollereau and co-workers cloned the gene for the human receptor [*FEBS Letters*, 341:33(1994)] and stably expressed that gene in CHO cells [*Nature*, 377:532(1995)]. One of the authors of the latter paper graciously provided a sample of those transgenic cells [referred to as recombinant CHO($hORL_1$) cells] for use by the present inventors.

Binding inhibition studies similar to those of Example 6 were carried out using 500,00 cells/mL in place of the membrane preparation using the N-benzyl-1,4,5-trisubstituted-2,3-diketopiperazine library. The results of those studies are shown in Table 12, below, for each library pool.

Table 12

N-Benzyl-1,4,5-trisubstituted-
2,3-diketopiperazine Library
Binding in hORL-CHO Cells



Pool No.	R^1	R^3	R^4	Mean	Minus NSB	1 % Bound
1	Fmoc-Ala	X	X	384	251.00	0.020
2	Fmoc -Phe	X	X	346	213.00	0.024
3	Fmoc-Gly	X	X	338.5	205.50	0.025
4	Fmoc-Ile	X	X	382.5	249.50	0.020
5	Fmoc-Lys(Boc)	X	X	233.35	100.35	0.050
6	Fmoc-Leu	X	X	391.55	258.55	0.019
7	Fmoc-Met(O)	X	X	351.05	218.05	0.023
8	Fmoc-Ser(tBut)	X	X	431.2	298.20	0.017
9	Fmoc-Thr(tBut)	X	X	491.7	358.70	0.014
10	Fmoc-Val	X	X	448.55	315.55	0.016
11	Fmoc-Tyr(tBut)	X	X	438.45	305.45	0.017
12	Fmoc-ala	X	X	366.1	233.10	0.022
13	Fmoc-phe	X	X	324.6	191.60	0.026
14	Fmoc-ile	X	X	399.75	266.75	0.019
15	Fmoc-lys(Boc)	X	X	188.35	55.35	0.091
16	Fmoc-leu	X	X	357.2	224.20	0.022
17	Fmoc-ser(tBut)	X	X	413.55	280.55	0.018
18	Fmoc-thr(tBut)	X	X	518.55	385.55	0.013
19	Fmoc-val	X	X	388.9	255.90	0.020
20	Fmoc-tyr(tBut)	X	X	424.25	291.25	0.017
21	Fmoc-Nle	X	X	341.2	208.20	0.024
22	Fmoc-nle	X	X	379.25	246.25	0.020
23	Fmoc-Nva	X	X	432.85	299.85	0.017
24	Fmoc-nva	X	X	380.9	247.90	0.020
25	Fmoc-NapAla	X	X	385.35	252.35	0.020
26	Fmoc-napala	X	X	355.3	222.30	0.023
27	Fmoc-Phg	X	X	476.05	343.05	0.015
28	Fmoc-ChAla	X	X	459.6	326.60	0.015
29	Fmoc-chala	X	X	426.65	293.65	0.017
30	X	Fmoc-Ala	X	245.7	112.70	0.045
31	X	Fmoc -Phe	X	402.85	269.85	0.019
32	X	Fmoc-Gly	X	308.65	175.65	0.029
33	X	Fmoc-Ile	X	316.5	183.50	0.027
34	X	Fmoc-Leu	X	373.2	240.20	0.021
35	X	Fmoc-Met(O)	X	372	239.00	0.021
36	X	Fmoc-Ser(tBut)	X	357.5	224.50	0.022
37	X	Fmoc-Thr(tBut)	X	340.05	207.05	0.024
38	X	Fmoc-Val	X	267.65	134.65	0.037
39	X	Fmoc-Tyr(tBut)	X	402.15	269.15	0.019

40	X	Fmoc-ala		X	299.1	166.10	0.030
41	X	Fmoc-phe		X	407.75	274.75	0.018
42	X	Fmoc-ile		X	328.85	195.85	0.026
43	X	Fmoc-leu		X	419.65	286.65	0.018
44	X	Fmoc-ser(tBut)		X	314.85	181.85	0.028
45	X	Fmoc-thr(tBut)		X	401.25	268.25	0.019
46	X	Fmoc-val		X	359.15	226.15	0.022
47	X	Fmoc-tyr(tBut)		X	522.25	389.25	0.013
48	X	Fmoc-Nle		X	300.3	167.30	0.030
49	X	Fmoc-nle		X	282.9	149.90	0.034
50	X	Fmoc-Nva		X	300.95	167.95	0.030
51	X	Fmoc-nva		X	438.65	305.65	0.016
52	X	Fmoc-NapAla		X	331.05	198.05	0.025
53	X	Fmoc-napala		X	340.05	207.05	0.024
54	X	Fmoc-Phg		X	256.9	123.90	0.041
55	X	Fmoc-ChAla		X	417.65	284.65	0.018
56	X	Fmoc-chala		X	341.55	208.55	0.024
57	X	X	1-Phenyl-1-cyclopropanecarboxylic Acid		299.95	166.95	0.030
58	X	X	m-Tolylacetic Acid		343.7	210.70	0.024
59	X	X	3-Fluorophenylacetic Acid		346.5	213.50	0.024
60	X	X	(α,α,α-Trifluoro-m-tolyl)acetic acid		290.45	157.45	0.032
61	X	X	p-Tolylacetic Acid		266.35	133.35	0.038
62	X	X	3-Methoxyphenylacetic Acid		385.3	252.30	0.020
63	X	X	4-Methoxyphenylacetic Acid		266.9	133.90	0.038
64	X	X	4-Ethoxyphenylacetic Acid		289.35	156.35	0.032
65	X	X	4-Isobutyl-α-methylphenyl-acetic Acid		351.45	218.45	0.023
66	X	X	3,4-Dichloro-phenylacetic Acid		238.4	105.40	0.048
67	X	X	3,5-Bis-(Trifluoro-methyl)phenyl-acetic Acid		306.4	173.40	0.029
68	X	X	Phenylacetic Acid		385.15	252.15	0.020
69	X	X	Hydrocinnamic Acid		367.45	234.45	0.021

70	X	X	4-Phenylbutyric Acid	366.4	233.40	0.022
71	X	X	Butyric Acid	369.1	236.10	0.021
72	X	X	Heptanoic Acid	293.6	160.60	0.031
73	X	X	Isobutyric Acid	284.25	151.25	0.033
74	X	X	Isovaleric Acid	369.95	236.95	0.021
75	X	X	4-Methylvaleric Acid	341.05	208.05	0.024
76	X	X	Trimethylacetic Acid	395.45	262.45	0.019
77	X	X	tert-Butylacetic Acid	394.35	261.35	0.019
78	X	X	Cyclohexanecarboxylic Acid	352.35	219.35	0.023
79	X	X	Cyclohexyl-acetic Acid	337.05	204.05	0.025
80	X	X	Cyclohexane-butyric Acid	325.15	192.15	0.026
81	X	X	Cycloheptanecarboxylic Acid	248.4	115.40	0.044
82	X	X	Acetic Acid	353.9	220.90	0.023
83	X	X	Cyclobutanecarboxylic Acid	399.7	266.70	0.019
84	X	X	Cyclopentanecarboxylic Acid	406.9	273.90	0.018
85	X	X	Cyclohexanepropionic Acid	412.35	279.35	0.018
86	X	X	4-Methyl-1-cyclo-hexanecarboxylic Acid	391.3	258.30	0.020
87	X	X	4-tert-Butyl-cyclohexane-carboxylic Acid	338.2	205.20	0.025
88	X	X	1-Adamantaneacetic Acid	235.75	102.75	0.049
89	X	X	3-3-Diphenylpropionic Acid	291.45	158.45	0.032
90	X	X	Dicyclohexyl-acetic Acid	271.9	138.90	0.036
91	X	X	Indole-3-acetic Acid	431.6	298.60	0.017
92	X	X	1-Naphthylacetic Acid	325.55	192.55	0.026
93	X	X	3-(3,4,5)-tri-methoxy-phenylpropionic Acid	410.1	277.10	0.018
94	X	X	2-Norbornane-acetic Acid	322.95	189.95	0.027
95	X	X	Cyclopentyl-acetic Acid	314.45	181.45	0.028
96	X	X	2-Ethyl butyric Acid	310.5	177.50	0.028

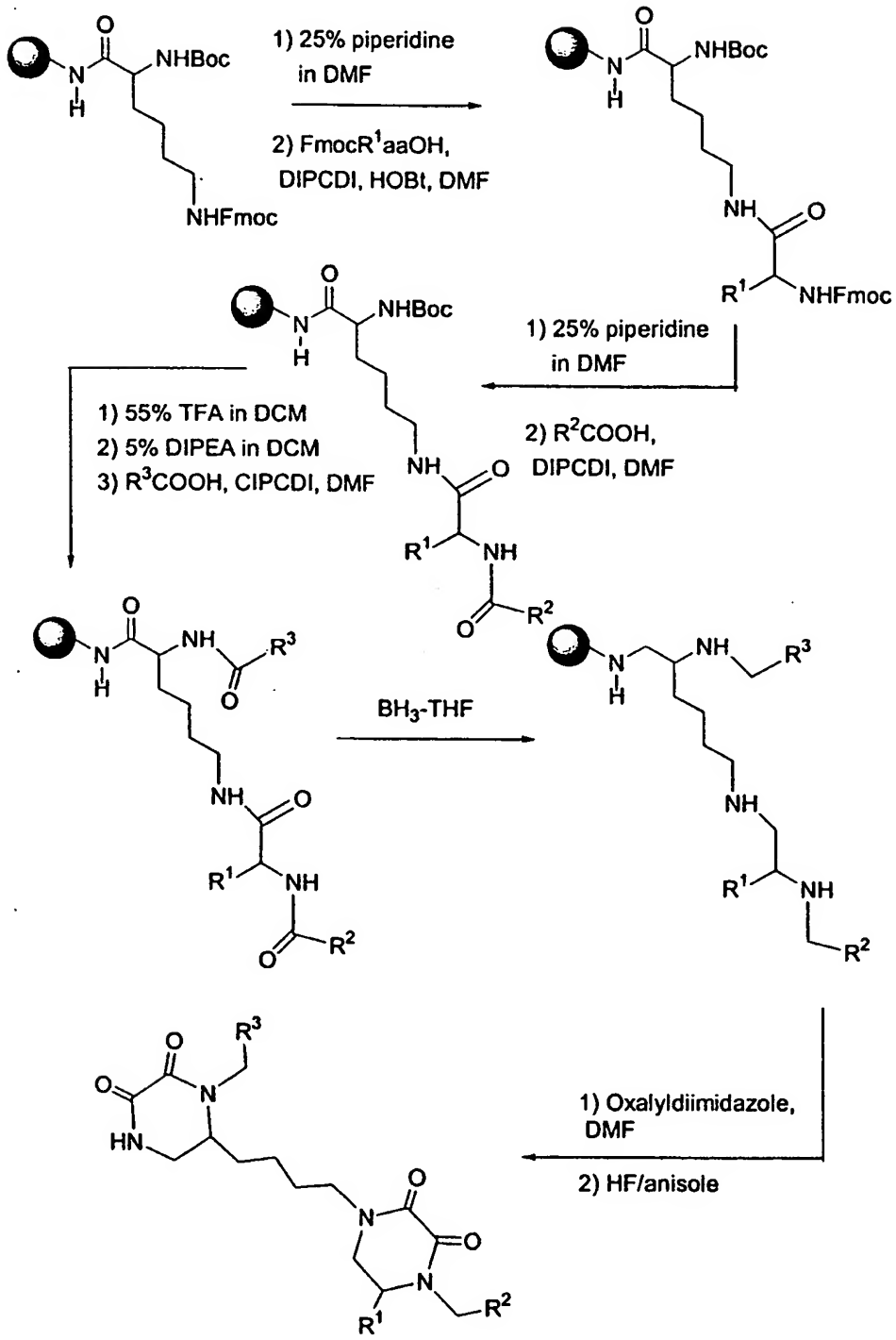
The results of a binding study such as that above are often graphed using the 1/(percent bound) data provided above. Again, scanning the data indicates that pools 5 and 15 provided the best binding for R^1, pools 30 and 54 provided best binding for R^3 and pools 66 and 88 provided best binding for R^4. Interestingly, pools 15 and 30 also provided the greatest inhibition in the orphanin binding assay of Example 6.

Example 9: Preparation of Bis-Diketodiazabicyclic Compounds and Bis-Diazacyclic Compounds

Bis-diketodiazabicyclic and bis-diazacyclic compounds and libraries are also contemplated here. Exemplary compounds have two carbonyl-containing rings or two ring nitrogen-containing rings linked to each other via a side chain of one of the R grooups of one of the rings such as a lysine or ornithine side chain. Scheme 8, below, illustrates an exemplary synthetic scheme that utilizes a lysine side chain.

An exemplary compound that was synthesized follows the Scheme and detained synthetic procedure.

Scheme 8


1) 25% piperidine in DMF
2) FmocR1aaOH, DIPCDI, HOBt, DMF
NHBoc
NHFmoc
1) 25% piperidine in DMF
1) 55% TFA in DCM
2) 5% DIPEA in DCM
3) R3COOH, CIPCDI, DMF
2) R2COOH, DIPCDI, DMF
BH3-THF
1) Oxalyldiimidazole, DMF
2) HF/anisole

Typical procedure for the Boc-Lys(Fmoc) coupling.

p-Methylbenzydrylamine (MBHA; 100 mg) resin (0.1 meq/g, 100-200 mesh) was contained within a sealed polypropylene mesh resin packet. Following neutralization with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM)(3x5ml), the resin was washed with DCM (3x5ml). A 0.5M solution of Boc-Lys(Fmoc) in DMF (6X, 0.6 meq total; 1.2 ml), 1.2 ml 0.5M 1-hydroxybenzotriazole (HOBt, 6X, 0.6 meq) in DMF, and 1.2 ml 0.5M diisopropylcarbodiimide (DIPCDI, 6X, 0.6 meq) in DMF was combined in a 10 ml polypropylene bottle. The resin packet was then added to the solution and permitted to react by shaking on a reciprocating shaker for 120 minutes. Following decanting of the reaction solution, the resin was washed with DMF (3x5ml).

Typical procedure for the second Fmoc-amino acid coupling.

The Fmoc side chain protecting group was then removed by treatment with 5 ml of 25% piperidine in DMF, followed by washes with DMF (3x5ml). A 0.5M solution of Fmoc-Phe in DMF (6X, 0.6 meq total; 1.2 ml), 1.2 ml 0.5M 1-hydroxybenzotriazole (HOBt, 6X, 0.6 meq) in DMF, and 1.2 ml 0.5M diisopropyl-carbodiimide (DIPCDI, 6X, 0.6 meq) in DMF was combined in a 10 ml polypropylene bottle. The resin packet was then added to the solution and permitted to react by shaking on a reciprocating shaker for 120 minutes. Following the reaction, the solution was decanted and the resin washed with DMF (3x5ml).

Typical procedure for the first carboxylic acid coupling.

Following deprotection of the Fmoc protecting group with 5 ml 25% piperidine in DMF for 30 minutes, the resin was washed twice with 5ml DMF. A 0.5M solution of phenyl acetic acid in DMF (10X, 1.0 meq total; 2.0 ml), 2.0 ml 0.5M 1-hydroxybenzotriazole (HOBt, 10X, 1.0 meq) in DMF, and 2.0 ml 0.5M diisopropylcarbodiimide (DIPCDI, 10X, 1.0 meq) in DMF was combined in a 10 ml polypropylene bottle. The resin packet was then added to the solution and permitted to react by shaking on reciprocation shaker for 120 minutes. Following the reaction, the solution was decanted and the resin washed with DMF (3x5ml).

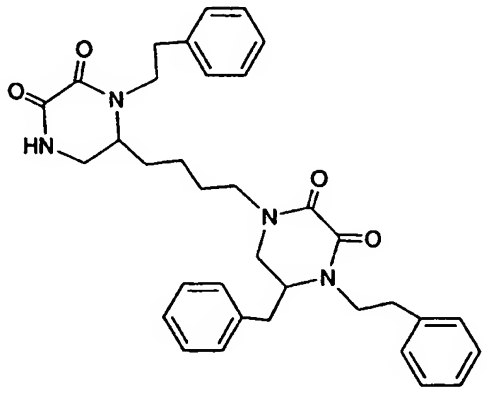
Typical procedure for a second carboxylic acid coupling.

Following deprotection of the Boc protecting group with 5 ml 55% TFA/DCM for 30 minutes, the resin was washed twice with 5ml DCM, 3 times with 5 ml isopropanol, and twice with 5 ml DCM. The resin packet was neutralized with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM) (3x5ml) and then washed with DCM (3x5ml). A 0.5M solution of phenyl acetic acid in DMF (10X, 1.0 meq total; 2.0 ml), 2.0 ml 0.5M 1-hydroxybenzotriazole (HOBt, 10X, 1.0 meq) in DMF, and 2.0 ml 0.5M diisopropylcarbodiimide (DIPCDI, 10X, 1.0 meq) in DMF was combined in a 10 ml polypropylene bottle. The resin packet was then

added to the solution and allowed to react by shaking on reciprocation shaker for 120 minutes. Following the reaction, the solution was decanted and the resin washed with DMF (3x5ml).

The resins were reduced, the diketopiperizines were formed, and the resins were cleaved as described in Examples 1 and 2.

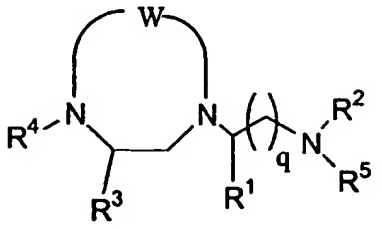
Using the above procedure and that of Scheme 8, a compound corresponding in structure to the formula below was prepared in which phenylacetic acid was used as R^2COOH and R^3COOH and FmocPhe was used as Fmoc-R1aa-OH



The foregoing description and the examples are intended as illustrative and are not to be taken as limiting. Still other variations within the spirit and scope of this invention are possible and will readily present themselves to those skilled in the art.

WHAT IS CLAIMED IS:

1. A compound having a structure corresponding to that shown in Formula I, below, or a pharmaceutically acceptable salt thereof:



I

wherein:

q is an integer having a value of 1-7;

W is a saturated or unsaturated chain of 2-4 carbon atoms that are bonded at each terminus of the chain to the depicted nitrogen atoms, wherein (1) zero, one or two of those carbon atoms of the chain is doubly bonded to an oxygen atom, (2)(a) each of the remaining carbon atoms of the chain is independently bonded to one or two substituents selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) two of those remaining carbon atoms of the chain form a saturated or unsaturated mono- or bicyclic ring containing 5-

to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur;

R^1 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^2 is selected from the group consisting of a C_1-C_{10} alkyl, C_2-C_{10} alkenyl, benzyl, substituted benzyl, naphthyl, or substituted naphthyl group and preferably is a methyl, ethyl, benzyl, allyl, and a naphthylmethyl group;

R^3 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{16} phenylalkyl, C_7-C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^4 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} substituted alkyl, C_3-C_7 substituted cycloalkyl, C_7-C_{16} phenylalkyl, C_7-C_{16} phenylalkenyl, C_7-C_{16} phenylalkenyl and a C_7-C_{16} substituted phenyl-alkenyl group; and

R^5 is selected from the group consisting of a hydrido, C_1-C_{10} acyl, aroyl, C_1-C_{10} alkylaminocarbonyl, C_1-C_{10} alkylthiocarbonyl,

arylaminocarbonyl, and an arylthiocarbonyl group.

2. The compound according to claim 1 wherein the carbon chain W contains one double bond.

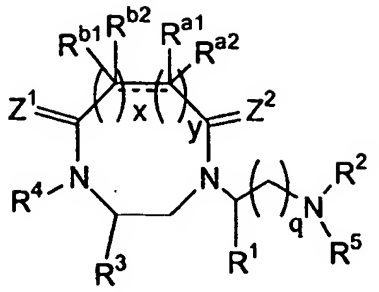
3. The compound according to claim 1 wherein the carbon chain W contains zero, one or two carbonyl groups.

4. The compound according to claim 3 wherein the carbon chain W contains one or two carbonyl groups that are arrayed symmetrically between the two depicted nitrogen atoms.

5. The compound according to claim 3 wherein two carbonyl groups are present, and each is bonded to a nitrogen atom forming two amide groups.

6. The compound according to claim 3 wherein one carbonyl group is present, and that carbonyl group is present as a keto group.

7. A compound having a structure corresponding to that shown in Formula II, below, or a pharmaceutically acceptable salt thereof:



II

wherein:

q is an integer that is one through seven;

each of $=Z^1$ and $=Z^2$ is independently $=O$ or $=Z^1$ is $-R^{c1}$ and $-R^{c2}$ and $=Z^2$ is $-R^{c3}$ and $-R^{c4}$, wherein $-R^{c1}$, $-R^{c2}$, $-R^{c3}$ and $-R^{c4}$ are independently selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

x and y are independently zero or one, and the sum of x + y is zero, one or two;

the dotted line between the carbon atom of R^{a1} and R^{a2} and the carbon atom of R^{b1} and R^{b2} indicates the presence or absence of one additional bond between those depicted carbon atoms, so that when present, the additional bond is shown as a solid line, following usual conventions of organic chemistry, and R^{a2} and R^{b2} are absent;

(a) R^{a1}, R^{a2}, R^{b1} and R^{b2} are independently selected from the group consisting of a hydrido, C_1-

C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) each of R^{a1} and R^{b1} is also bonded to the same saturated or unsaturated mono- or bicyclic ring that contains 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur, or (c) one or both of R^{a1} and R^{a2} and R^{b1} and R^{b2} together are =O, and wherein R^{a2} and R^{b2} are absent when a double bond is present between the depicted carbon atoms;

R^1 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^2 is selected from the group consisting of a C_1-C_{10} alkyl, C_2-C_{10} alkenyl, benzyl, substituted benzyl, naphthyl, and a substituted naphthyl group;

R^3 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{16} phenylalkyl, C_7-C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^4 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10}

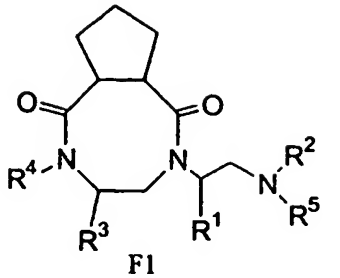
substituted alkyl, C_3-C_7 substituted cycloalkyl, C_7-C_{16} phenylalkyl, C_7-C_{16} phenylalkenyl, C_7-C_{16} phenylalkenyl and a C_7-C_{16} substituted phenyl-alkenyl group; and

R^5 is selected from the group consisting of a hydrido, C_1-C_{10} acyl, aroyl, C_1-C_{10} alkylaminocarbonyl, C_1-C_{10} alkylthiocarbonyl, arylaminocarbonyl, and an arylthiocarbonyl group.

8. The compound according to claim 7 wherein x and y are one, and the sum of x + y is two.

9. The compound according to claim 8 wherein each of R^{a1} and R^{b1} is also bonded to the same saturated or unsaturated mono- or bicyclic ring that contains 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur.

10. The compound according to claim 9 that corresponds in structure to a formula below



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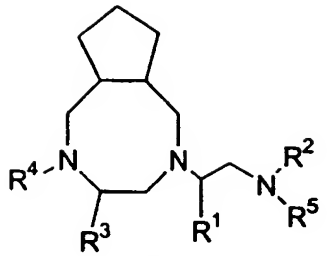

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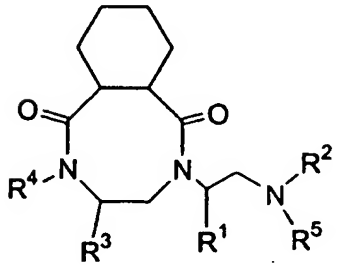

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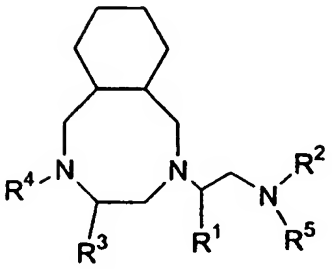

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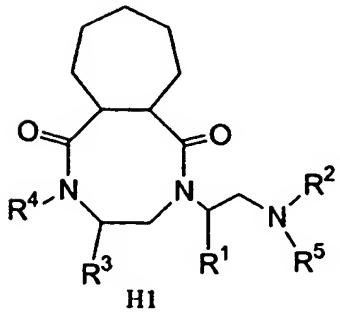

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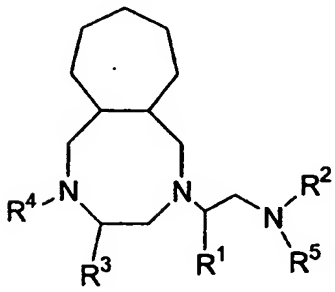

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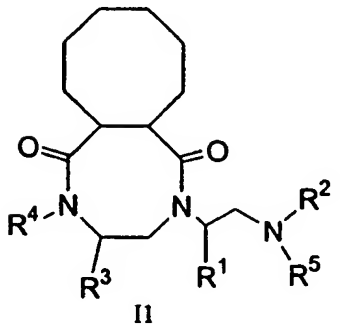

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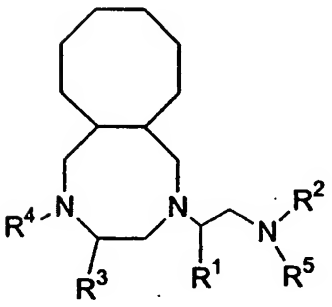

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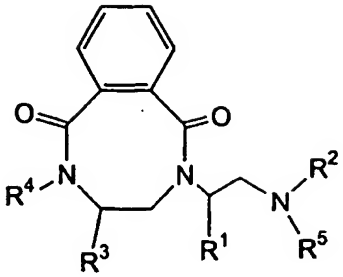

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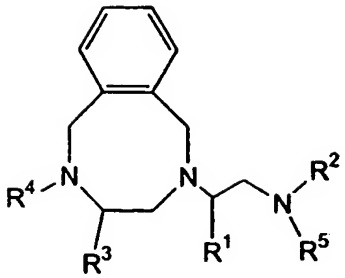

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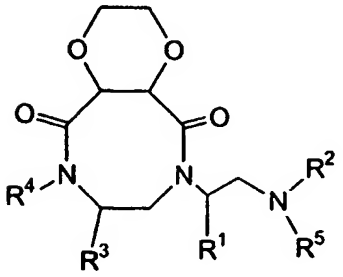

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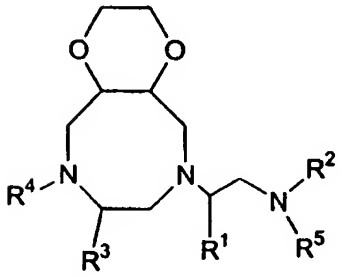

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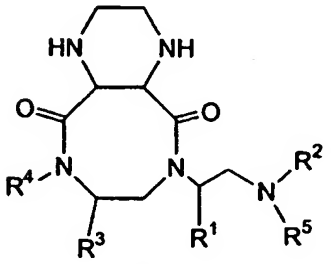

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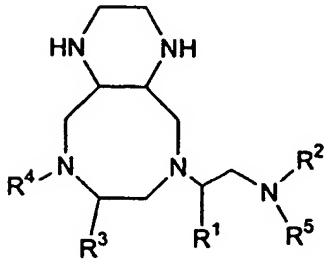

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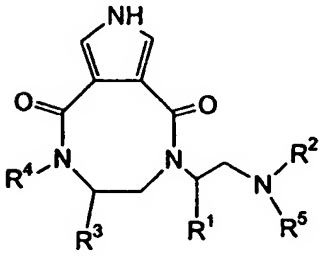

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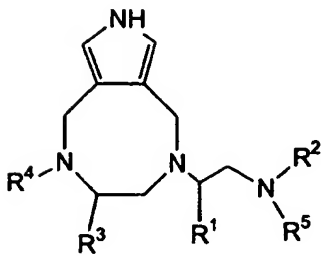

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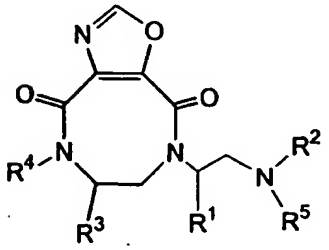

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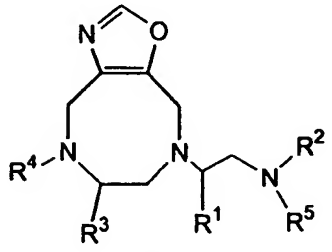

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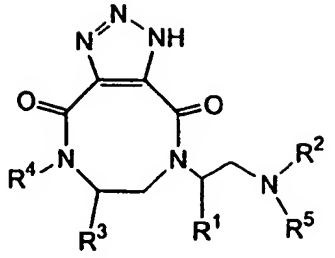
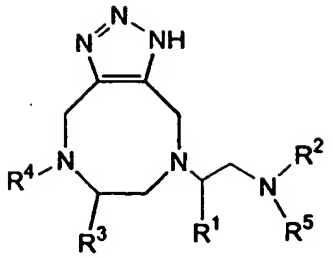


O1



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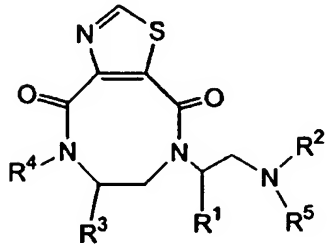
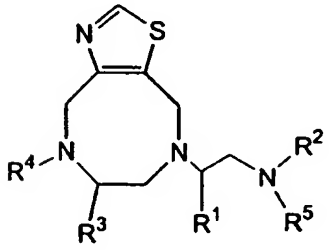


P1



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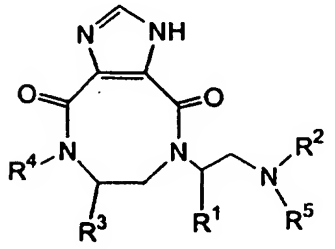
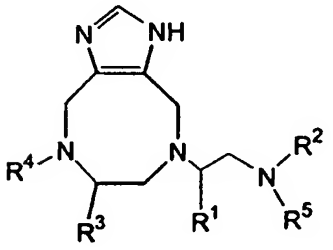
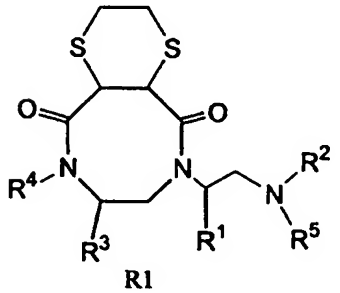


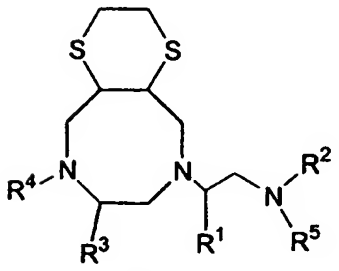
Q1



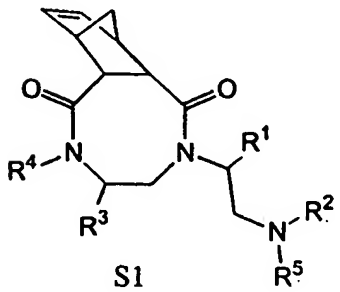
Q2



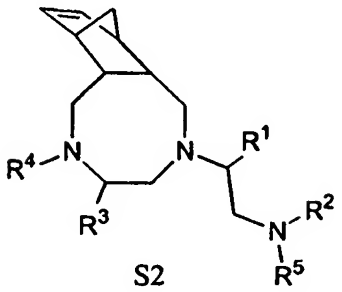
R1



R2



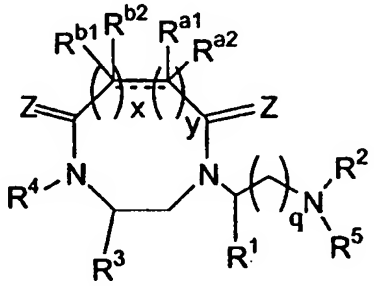
S1



S2

11. The compound according to claim 7 wherein x and y are zero, and the sum of x + y is zero.

12. A compound having a structure corresponding to that shown in Formula III, below, or a pharmaceutically acceptable salt thereof:



III

wherein:

=Z is =O or $(-H)_2$;

R^{a2} and R^{b2} are hydrido or are absent;

q is an integer that is one through seven;

x and y are independently zero or one, and the sum of x + y is zero, one or two;

the dotted line between the carbon atom of R^{a1} and R^{a2} and the carbon atom of R^{b1} and R^{b2} indicates the presence or absence of one additional bond between those depicted carbon atoms, so that when present, the additional bond is shown as a solid line, following usual conventions of organic chemistry, and R^{a2} and R^{b2} are absent;

(a) R^{a1}, R^{a2}, R^{b1} and R^{b2} are independently selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) each of R^{a1} and R^{b1} is also bonded to the same saturated or unsaturated mono- or bicyclic ring that contains 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur, or (c) one or both of R^{a1} and R^{a2} and R^{b1} and R^{b2} together are =O, and wherein R^{a2} and R^{b2} are absent when a double bond is present between the depicted carbon atoms;

R^1 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^2 is selected from the group consisting of a C_1-C_{10} alkyl, C_2-C_{10} alkenyl, benzyl, substituted benzyl, naphthyl, and a substituted naphthyl group;

R^3 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{16} phenylalkyl, C_7-C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^4 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} substituted alkyl, C_3-C_7 substituted cycloalkyl, C_7-C_{16} phenylalkyl, C_7-C_{16} phenylalkenyl, C_7-C_{16} phenylalkenyl and a C_7-C_{16} substituted phenyl-alkenyl group; and

R^5 is selected from the group consisting of a hydrido, C_1-C_{10} acyl, aroyl, C_1-C_{10} alkylaminocarbonyl, C_1-C_{10} alkylthiocarbonyl, arylaminocarbonyl, and an arylthiocarbonyl group.

13. The compound according to claim 12 wherein x and y are one, and the sum of x + y is two.

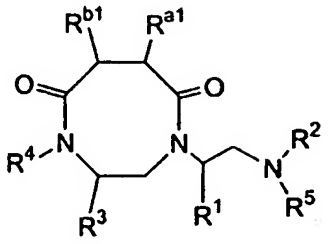
14. The compound according to claim 13 wherein each of R^{a1} and R^{b1} is also bonded to the same saturated or unsaturated mono- or bicyclic ring that contains 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur.

15. The compound according to claim 12 wherein R^2 is methyl, benzyl or naphthylmethyl.

16. The compound according to claim 12 wherein x and y are zero, and the sum of x + y is zero.

17. The compound according to claim 12 wherein q is one.

18. The compound according to claim 17 that corresponds in structure to a formula below



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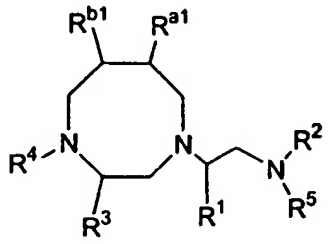

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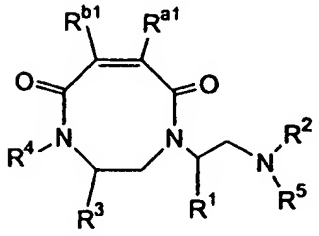

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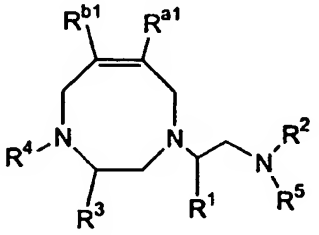

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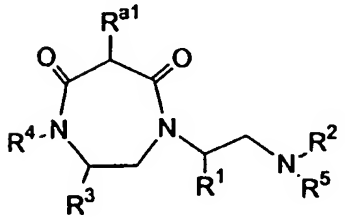
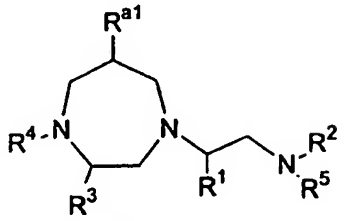


D1



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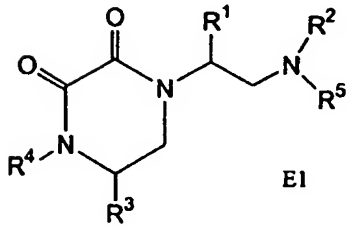

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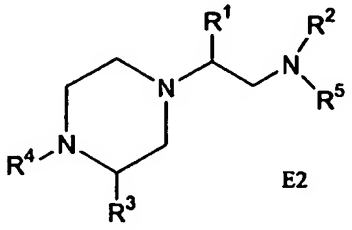

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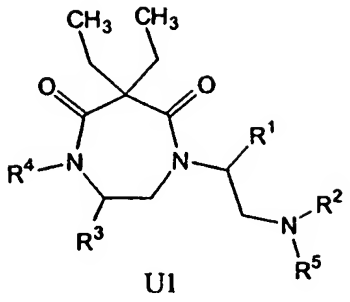

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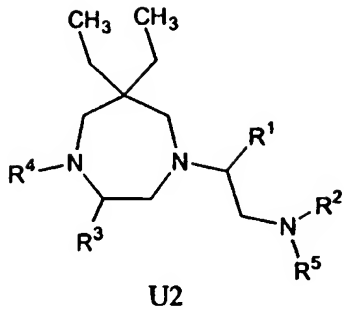

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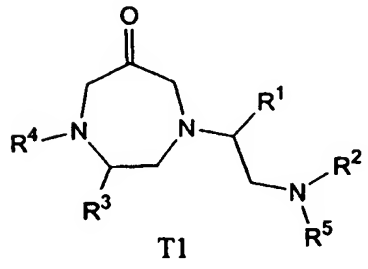
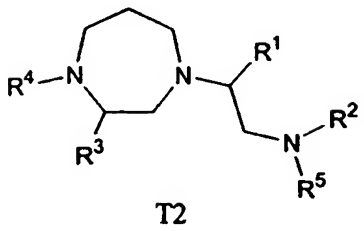


T1



T2

19. The compound according to claim 18 wherein

R^1 is selected from the group consisting of a hydrido, methyl, benzyl, 2-butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^2 is methyl;

R^3 is selected from the group consisting of a hydrido, methyl, benzyl, 3-hydroxypropyl, 2-butyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl,4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^4 is selected from the group consisting of a 1-phenyl-1-cyclopropylmethyl, *m*-tolylethyl, 3-fluorophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 3-methoxyphenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, butyl, heptyl, isobutyryl, isovaleryl, 4-methylvaleryl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropyl-methyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclo-hexylethyl, 1-adamantylethyl, 3,3-diphenylpropyl, cyclopentylethyl, 2,2-dicyclohexylethyl, 2-indol-3-ylethyl, 1-naphthylethyl, 3-(3,4,5-trimethoxyphenyl)-propyl, 2-norbornylethyl, cyclopentylethyl, a 2-ethylbutyl substituent; and

R^5 is hydrido.

20. The compound according to claim 18 wherein

R^1 is selected from the group consisting of a hydrido, methyl, benzyl, 2-butyl, N-methyl,N-benzylaminobutyl, N-methylaminobutyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl,hydroxymethyl, 1-hydroxyethyl, 2-propyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

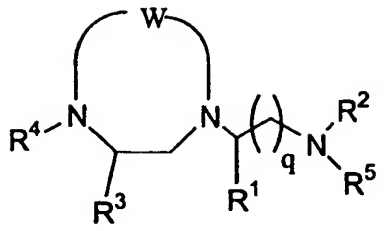
R^2 is benzyl;

R^3 is selected from the group consisting of a hydrido, methyl, benzyl, 3-hydroxypropyl, 2-butyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl,4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^4 is selected from the group consisting of a 1-phenyl-1-cyclopropylmethyl, *m*-tolylethyl, 3-fluorophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 3-methoxyphenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, butyl, heptyl, isobutyryl, isovaleryl, 4-methylvaleryl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropyl-methyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclo-hexylethyl, 1-adamantylethyl, 3,3-diphenylpropyl, cyclopentylethyl, 2,2-dicyclohexylethyl, 2-indol-3-ylethyl, 1-naphthylethyl, 3-(3,4,5-trimethoxy-phenyl)propyl, 2-norbornylethyl, cyclopentylethyl, and a 2-ethylbutyl substituent; and

R^5 is hydrido.

21. A library of compounds having a structure corresponding to that shown in Formula I, below, or a pharmaceutically acceptable salt thereof:



I

wherein:

q is an integer having a value of 1-7;

W is a saturated or unsaturated chain of 2-4 carbon atoms that are bonded at each terminus of the chain to the depicted nitrogen atoms, wherein (1) zero, one or two of those carbon atoms of the chain is doubly bonded to an oxygen atom, (2)(a) each of the remaining carbon atoms of the chain is independently bonded to one or two substituents selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) two of those remaining carbon atoms of the chain form a saturated or unsaturated mono- or bicyclic ring containing 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur;

R^1 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl,

phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^2 is selected from the group consisting of a C_1-C_{10} alkyl, C_2-C_{10} alkenyl, benzyl, substituted benzyl, naphthyl, or substituted naphthyl group and preferably is a methyl, ethyl, benzyl, allyl, and a naphthylmethyl group;

R^3 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{16} phenylalkyl, C_7-C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^4 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} substituted alkyl, C_3-C_7 substituted cycloalkyl, C_7-C_{16} phenylalkyl, C_7-C_{16} phenylalkenyl, C_7-C_{16} phenylalkenyl and a C_7-C_{16} substituted phenyl-alkenyl group; and

R^5 is selected from the group consisting of a hydrido, C_1-C_{10} acyl, aroyl, C_1-C_{10} alkylaminocarbonyl, C_1-C_{10} alkylthiocarbonyl, arylaminocarbonyl, and an arylthiocarbonyl group.

22. The library according to claim 21 wherein the carbon chain W contains one double bond.

23. The library according to claim 21 wherein

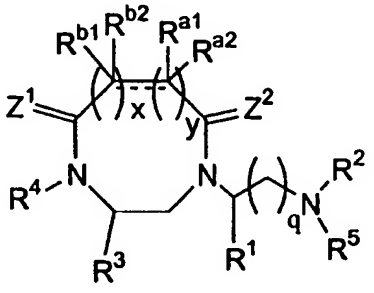
the carbon chain W contains zero, one or two carbonyl groups.

24. The library according to claim 23 wherein the carbon chain W contains one or two carbonyl groups that are arrayed symmetrically between the two depicted nitrogen atoms.

25. The library according to claim 23 wherein two carbonyl groups are present, and each is bonded to a nitrogen atom forming two amide groups.

26. The library according to claim 23 wherein one carbonyl group is present, and that carbonyl group is present as a keto group.

27. A library of compounds having a structure corresponding to that shown in Formula II, below, or a pharmaceutically acceptable salt thereof:



II

wherein:

q is an integer that is one through seven;

each of $=Z^1$ and $=Z^2$ is independently =O or $=Z^1$ is $-R^{c1}$ and $-R^{c2}$ and $=Z^2$ is $-R^{c3}$ and $-R^{c4}$, wherein $-R^{c1}$, $-R^{c2}$, $-R^{c3}$ and $-R^{c4}$ are independently selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

x and y are independently zero or one, and the sum of x + y is zero, one or two;

the dotted line between the carbon atom of R^{a1} and R^{a2} and the carbon atom of R^{b1} and R^{b2} indicates the presence or absence of one additional bond between those depicted carbon atoms, so that when present, the additional bond is shown as a solid line, following usual conventions of organic chemistry, and R^{a2} and R^{b2} are absent;

(a) R^{a1}, R^{a2}, R^{b1} and R^{b2} are independently selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) each of R^{a1} and R^{b1} is also bonded to the same saturated or unsaturated mono- or bicyclic ring that contains 5- to 8-members in each ring and zero to three

heteroatoms in each ring that are independently oxygen, nitrogen or sulfur, or (c) one or both of R^{a1} and R^{a2} and R^{b1} and R^{b2} together are =O, and wherein R^{a2} and R^{b2} are absent when a double bond is present between the depicted carbon atoms;

R^1 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^2 is selected from the group consisting of a C_1-C_{10} alkyl, C_2-C_{10} alkenyl, benzyl, substituted benzyl, naphthyl, and a substituted naphthyl group;

R^3 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{16} phenylalkyl, C_7-C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^4 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} substituted alkyl, C_3-C_7 substituted cycloalkyl, C_7-C_{16} phenylalkyl, C_7-C_{16} phenylalkenyl, C_7-C_{16} phenylalkenyl and a C_7-C_{16} substituted phenyl-alkenyl group; and

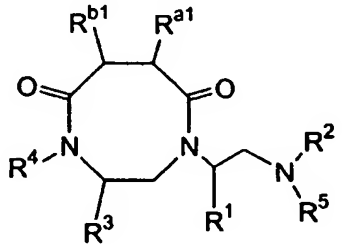
R^5 is selected from the group consisting of a hydrido, C_1-C_{10} acyl, aroyl, C_1-C_{10}

alkylaminocarbonyl, C_1-C_{10} alkylthiocarbonyl, arylaminocarbonyl, and an arylthiocarbonyl group.

28. The library according to claim 27 wherein x and y are one, and the sum of x + y is two.

29. The library according to claim 28 wherein each of R^{a1} and R^{b1} is also bonded to the same saturated or unsaturated mono- or bicyclic ring that contains 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur.

30. The library according to claim 29 in which the compounds correspond in structure to a formula bellow



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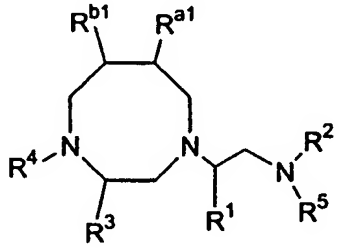

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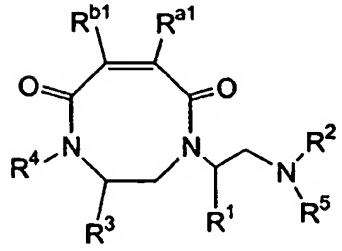

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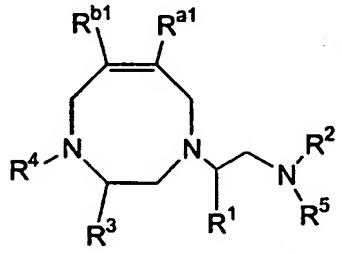

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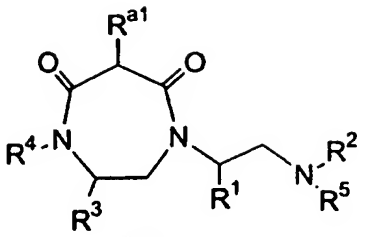
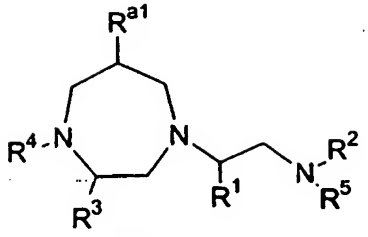


D1



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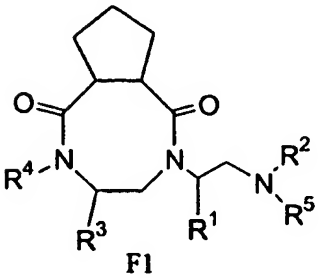
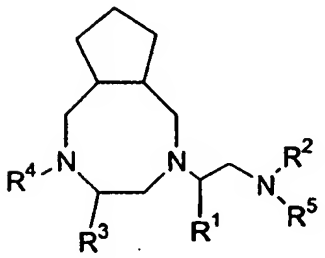


F1



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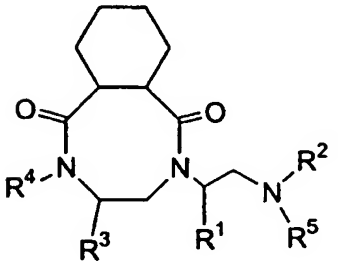
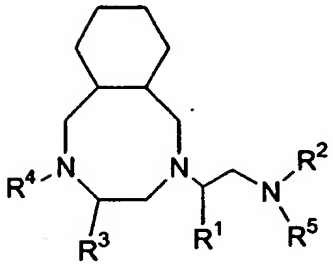


G1



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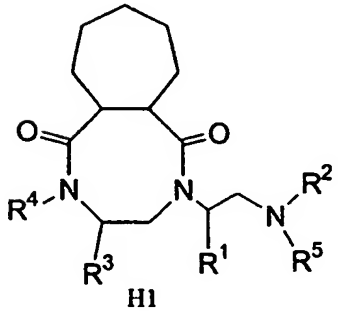

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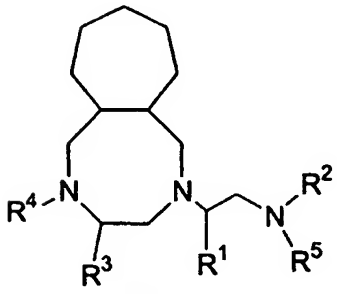

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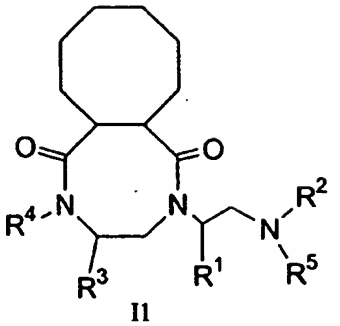
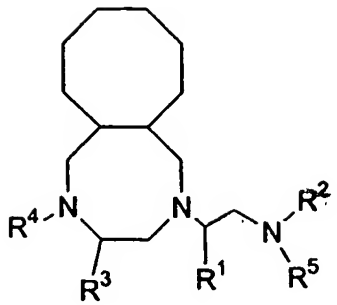


I1



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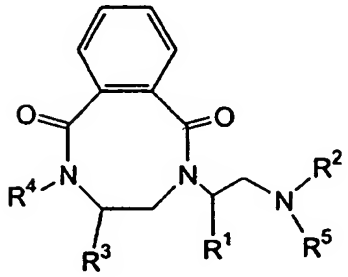

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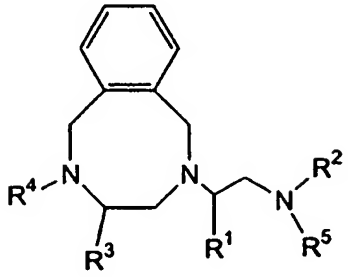

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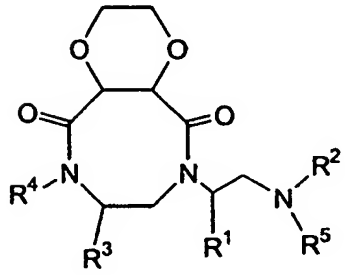
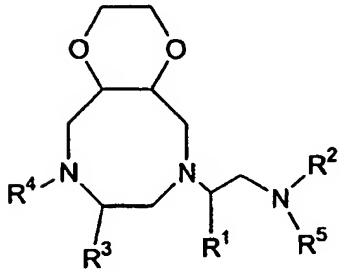
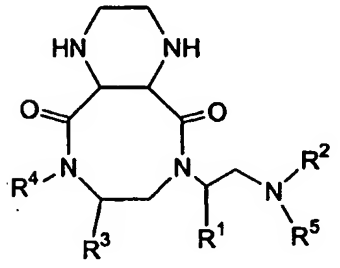


K1



K2



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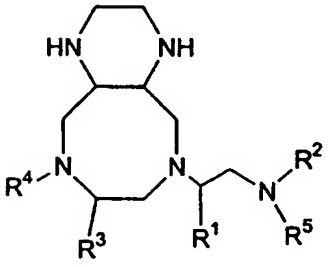

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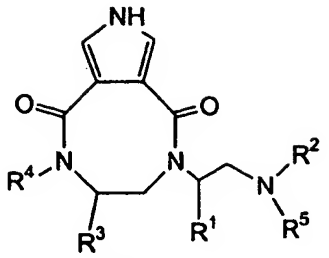

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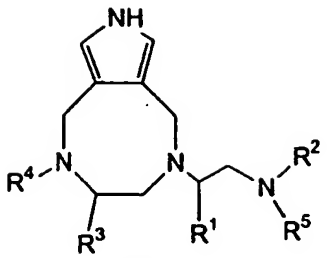
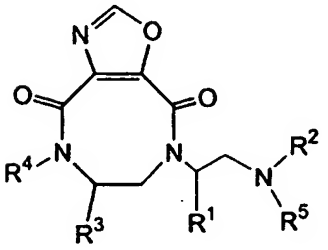


M2



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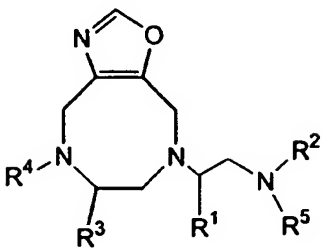

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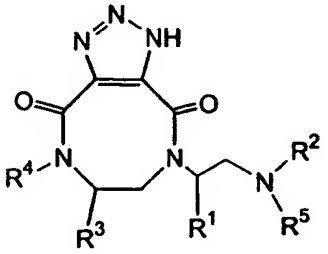
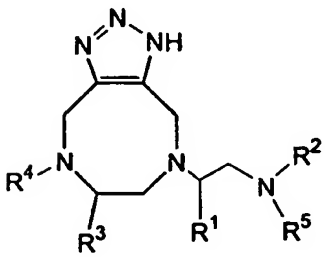


O1



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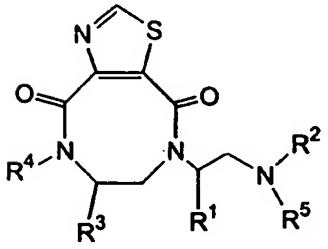

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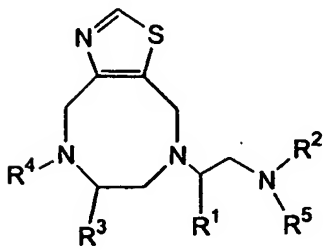
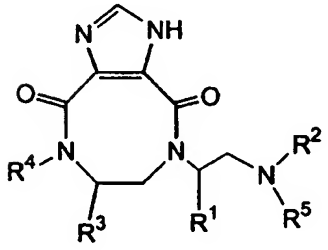
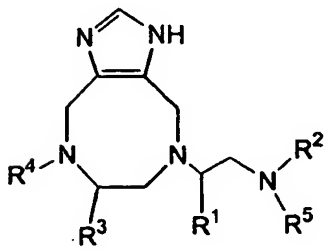


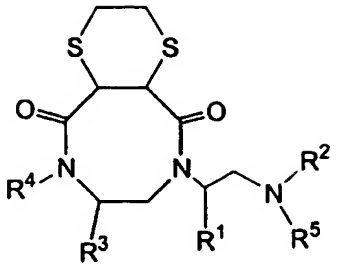
P2



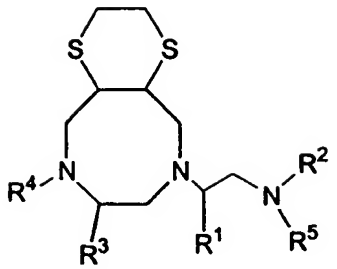
Q1



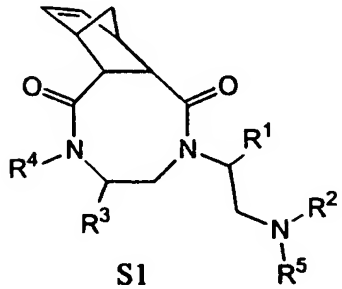
Q2



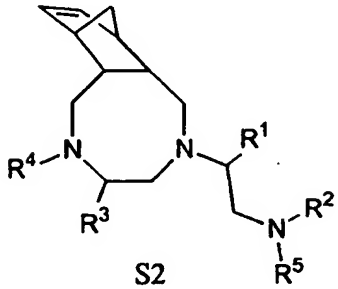
R1



R2



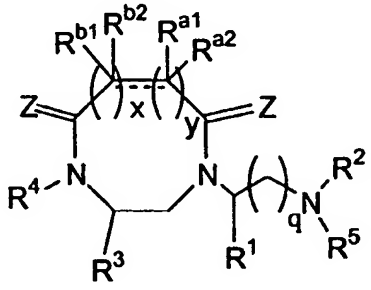
S1



S2

31. The library according to claim 27 wherein x and y are zero, and the sum of x + y is zero.

32. A library of compounds having a structure corresponding to that shown in Formula III, below, or a pharmaceutically acceptable salt thereof:



III

wherein:

=Z is =O or $(-H)_2$;

R^{a2} and R^{b2} are hydrido or are absent;

q is an integer that is one through seven;

x and y are independently zero or one, and the sum of x + y is zero, one or two;

the dotted line between the carbon atom of R^{a1} and R^{a2} and the carbon atom of R^{b1} and R^{b2} indicates the presence or absence of one additional bond between those depicted carbon atoms, so that when present, the additional bond is shown as a solid line, following usual conventions of organic chemistry, and R^{a2} and R^{b2} are absent;

(a) R^{a1}, R^{a2}, R^{b1} and R^{b2} are independently selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group or (b) each of R^{a1} and R^{b1} is also bonded to the same saturated or unsaturated mono- or bicyclic ring that contains 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur, or (c) one or both of R^{a1} and R^{a2} and R^{b1} and R^{b2} together are =O, and wherein R^{a2} and R^{b2} are absent when a double bond is present between the depicted carbon atoms;

R^1 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-

C_{10} phenylalkyl, C_7-C_{16} substituted phenyalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^2 is selected from the group consisting of a C_1-C_{10} alkyl, C_2-C_{10} alkenyl, benzyl, substituted benzyl, naphthyl, and a substituted naphthyl group;

R^3 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_1-C_{10} substituted alkyl, C_1-C_{16} phenylalkyl, C_7-C_{16} substituted phenylalkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, and a C_3-C_7 substituted cycloalkyl group;

R^4 is selected from the group consisting of a hydrido, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} substituted alkyl, C_3-C_7 substituted cycloalkyl, C_7-C_{16} phenylalkyl, C_7-C_{16} phenylalkenyl, C_7-C_{16} phenylalkenyl and a C_7-C_{16} substituted phenyl-alkenyl group; and

R^5 is selected from the group consisting of a hydrido, C_1-C_{10} acyl, aroyl, C_1-C_{10} alkylaminocarbonyl, C_1-C_{10} alkylthiocarbonyl, arylaminocarbonyl, and an arylthiocarbonyl group.

33. The library according to claim 32 wherein x and y are one, and the sum of x + y is two.

34. The library according to claim 33 wherein

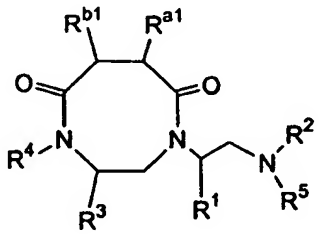
each of R^{a1} and R^{b1} is also bonded to the same saturated or unsaturated mono- or bicyclic ring that contains 5- to 8-members in each ring and zero to three heteroatoms in each ring that are independently oxygen, nitrogen or sulfur.

35. The library according to claim 32 wherein R^2 is methyl, benzyl or naphthylmethyl.

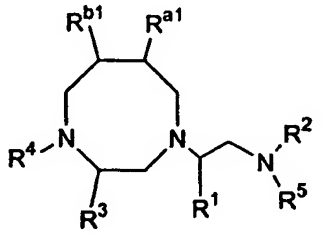
36. The library according to claim 32 wherein x and y are zero, and the sum of x + y is zero.

37. The library according to claim 32 wherein q is one.

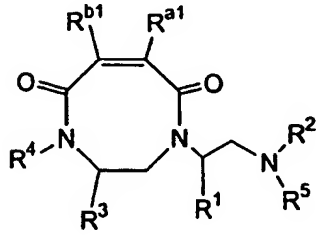
38. The library according to claim 37 that corresponds in structure to a formula below



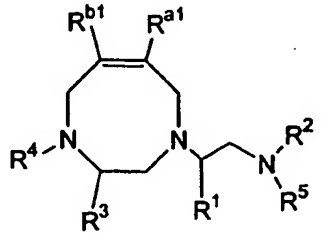
B1



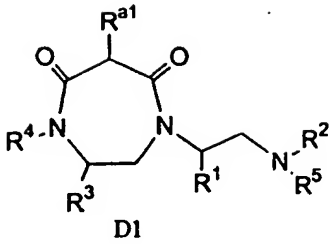
B2



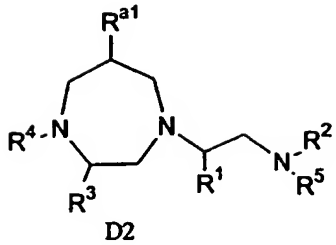
C1



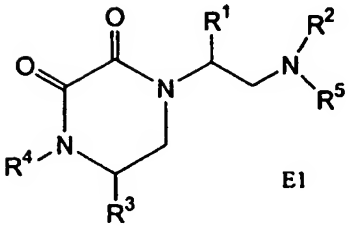
C2



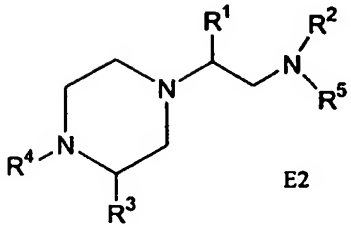
D1



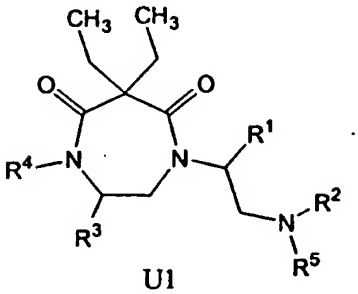
D2



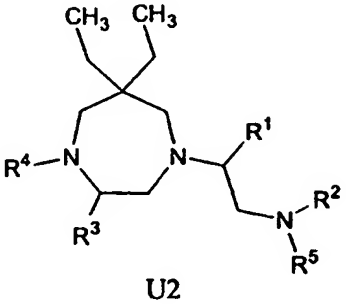
E1



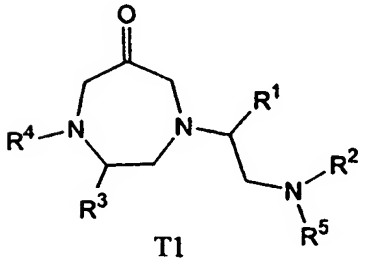
E2



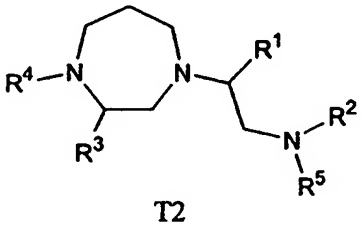
U1



U2



T1



T2

39. The compound according to claim 38 wherein R^1 is selected from the group consisting of a hydrido, methyl, benzyl, 2-butyl, N,N-dimethylaminobutyl, N-methylaminobutyl, 2-

methylpropyl, methylsulfinylethyl, methylthioethyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^2 is methyl;

R^3 is selected from the group consisting of a hydrido, methyl, benzyl, 3-hydroxypropyl, 2-butyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl,4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^4 is selected from the group consisting of a 1-phenyl-1-cyclopropylmethyl, *m*-tolylethyl, 3-fluorophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 3-methoxyphenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, butyl, heptyl, isobutyryl, isovaleryl, 4-methylvaleryl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropyl-methyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-*tert*-butyl-1-cyclohexylmethyl, 4-methylcyclo-hexylethyl, 1-adamantylethyl, 3,3-diphenylpropyl, cyclopentylethyl, 2,2-dicyclohexylethyl, 2-indol-3-ylethyl, 1-naphthylethyl, 3-(3,4,5-trimethoxyphenyl)-propyl, 2-norbornylethyl, cyclopentylethyl, a 2-ethylbutyl substituent; and

R^5 is hydrido.

40. The library according to claim 38 wherein

R^1 is selected from the group consisting of a hydrido, methyl, benzyl, 2-butyl, N-methyl,N-benzylaminobutyl, N-methylaminobutyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl,hydroxymethyl, 1-hydroxyethyl, 2-propyl, 4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^2 is benzyl;

R^3 is selected from the group consisting of a hydrido, methyl, benzyl, 3-hydroxypropyl, 2-butyl, 2-methylpropyl, methylsulfinylethyl, methylthioethyl, hydroxymethyl, 1-hydroxyethyl, 2-propyl,4-hydroxybenzyl, propyl, butyl, cyclohexylmethyl, phenyl, and a 2-naphthylmethyl substituent;

R^4 is selected from the group consisting of a 1-phenyl-1-cyclopropylmethyl, *m*-tolylethyl, 3-fluorophenethyl, (α,α,α-trifluoro-*m*-tolyl)ethyl, *p*-tolylethyl, 3-methoxyphenethyl, 4-methoxyphenethyl, 4-ethoxyphenethyl, 4-isobutyl-α-methylphenethyl, 3,4-dichlorophenethyl, 3,5-bis(trifluoromethyl)phenethyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, butyl, heptyl, isobutyryl, isovaleryl, 4-methylvaleryl, cyclohexylmethyl, cyclohexylethyl, cyclohexylbutyl, cycloheptylmethyl, ethyl, 2-methyl-1-cyclopropyl-methyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexanepropyl, 4-methyl-1-cyclohexylmethyl, 4-

tert-butyl-1-cyclohexylmethyl, 4-methylcyclohexylethyl, 1-adamantylethyl, 3,3-diphenylpropyl, cyclopentylethyl, 2,2-dicyclohexylethyl, 2-indol-3-ylethyl, 1-naphthylethyl, 3-(3,4,5-trimethoxyphenyl)propyl, 2-norbornylethyl, cyclopentylethyl, and a 2-ethylbutyl substituent; and

R^5 is hydrido.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/10841

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :436/518, 536; 540/358+, 450+, 473+, 484+, 490+
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/518, 536; 540/358+, 450+, 473+, 484+, 490+.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN Express, including: BIOSIS; US PATFULL, MARPAT, CAS ONLINE: REGISTRY, CAPLUS, CAOLD

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GORDON et al. Applications of Combinatorial Technologies to Drug Discovery. 1. Background and Peptide Libraries, J. Med. Chem. 29 April 1994, Vol. 37, No. 9, pages 1233-1251.	21-40
A	GORDON et al. Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies, and Future Directions. J. Med. Chem. 13 May 1994, Vol. 37, No. 10, pages 1385-1401.	21-40
A	TERRETT et al. Combinatorial Synthesis - The Design of Compound Libraries and Their Application to Drug Discovery. Tetrahedron. 1995, Vol. 51, No. 30, pages 8135-8173, especially page 8158.	1-40

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 14 JUNE 2000	Date of mailing of the international search report 04 AUG 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer GRACE HSU, PH.D. Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/10841

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GORDON et al. Reductive Alkylation on a Solid Phase: Synthesis of a Piperazinedione Combinatorial Library. Bioorg. & Med. Chem. Lett. 1995, Vol. 5, No. 1, pages 47-50.	1-40
A	WO 96/40202 A1 (CHIRON CORP.) 19 December 1996 (19/12/96), see entire document, especially page 79, lines 7-33 and pages 122-133.	1-40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/10841

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C07D 223/00, 225/00, 241/04, 245/00, 267/02; G01N 33/536, 33/543